

# SEXUALLY TRANSMITTED INFECTIONS

Second Edition

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**Somesh Gupta**  
**Bhushan Kumar**

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Charlotte A. Gaydos, Christopher Fairley, Darren Russell,  
Graham Neilsen, Janak K. Maniar, Jonathan Ross,  
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# Sexually Transmitted Infections



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## 2nd edition

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# Foreword

The Second Edition of “Sexually Transmitted Infections” represents a very substantial and useful contribution to the STI field, which today confronts many growing challenges. There has been continuing discovery of new sexually transmitted pathogens, in part through research and application of new technologies, and in part through emergence of new pathogens, such as HIV. A field that 50 years ago focused on five “venereal diseases” (gonorrhea, syphilis, chancroid, LGV, and granuloma inguinale), now encompasses over 30 different STI pathogens, with continuing emergence of many new variants or subspecies of these pathogens. We also recognize at least 30 different STI-related syndromes with most human organ systems affected by one or more STIs. There has been a disturbing resurgence of STIs in some populations over the past decade, coupled with declining susceptibility or outright resistance of major STI pathogens to important antimicrobial agents.

On the positive side, we do have many exciting new tools and approaches to provide evidence-based, cost-effective diagnosis, treatment and prevention for virtually all STIs. An objective of this textbook is to enable generalists and specialists from clinical, laboratory, and public health disciplines to understand and use modern tools and approaches appropriately. It is less and less acceptable today to sit back in a clinic to wait for the patient with an easily recognized or curable STI to appear at the door, undergo a few expensive tests, and return in a few days for single-dose curative treatment. There is a wide array of clinical presentations, etiologic possibilities, diagnostic and screening options, therapeutic challenges, multi-component prevention needs, health systems to be navigated, socio-behavioral risk factors;

and sex networks involving many diverse vulnerable populations require preventative interventions. All of this demands that health workers across many disciplines, STI program managers, and policy makers have accurate knowledge and understanding of STI, based upon up-to-date comprehensive sources of information.

Increasingly, answers to specific questions come from e-publications, easily accessed by computers and by smart phones. At the same time, there are great benefits to be gained from an integrated scientific overview that pulls together systematic advances together with authoritative but practical approaches.

With a growing number of highly distinguished authors representing many disciplines from throughout the world, this Second Edition of “Sexually Transmitted Infections” not only maintains its status as the best such STI textbook from India, with nearly a fifth of the world’s population, but ranks among the most authoritative STI textbook globally. I am honored to offer congratulations to the editors and authors Somesh Gupta and Bhushan Kumar and to the Section Editors for undertaking and executing what I know has been a huge but very rewarding task.

I am sure the book will be a great source of information and education to all who are involved with diagnosis, treatment, and/or prevention of sexually transmitted infections.

**Professor King Holmes**

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# Preface

Before the publication of the first edition of this book, no comprehensive reference text on the subject had ever been published from South Asia, particularly from India. Our goal in the first edition was to bring out a book with a definitive and fresh approach to the subject of Sexually Transmitted Infections (STIs). As the book was received well, we felt an imperative to provide a revised edition. We have been privileged to have received contributions from authors from many corners of the world, which makes this second edition truly international.

Our challenge in this edition was to distill the large amount of available knowledge on epidemiology, microbiology, physiology, molecular biology and therapeutics into a complete and scholarly presentation. To achieve such relevance, thoroughness, and practicality required a unique combination of scientific knowledge and clinical familiarity, best represented by the “academic physician”. Could the two of us have been able to do full justice to this? Obviously not. We, therefore, decided to divide the book into sections, and choose from the respective fields the experts to overlook these sections. They not only helped guide the style and content of the sections but also helped us find some of the best academicians and scientific physicians to contribute. Sharing this responsibility brought the best out of everyone and helped create a text that is truly encyclopedic, yet readable and accessible to all levels of readers.

Thus, the book has been reorganized, reformatted and substantially rewritten, with many new authors; it includes many new chapters, including those on social and legal issues, sexual abuse, and sexual dysfunction. The new edition covers clinical advances as well as issues that are becoming increasingly vital to STI specialists. We hope, it reflects the current state of science, practice, and the art of “Venereology”. Integration of basic and clinical sciences and therapeutics remain the highlight of the book. In a primarily clinical reference text, the space devoted to basic sciences must necessarily be restricted. However, a special effort has been made to ensure that these are reasonably easily understood by physicians whose interests and experience are primarily clinical. The effectiveness of any physician in practice ultimately depends on his ability to make an accurate diagnosis. Clinical descriptions have also been attempted to be as comprehensive as possible with many photographs, figures, and illustrations.

Many from the team who contributed to the first edition have also been included in the second edition. We would like to express our sincere gratitude for their efforts, which provided the framework upon which this edition has been expanded. We are also indebted to some of the previous edition contributors who generously allowed their material to be retained for the present edition, and also to those colleagues who donated color photographs.

It has been an exciting challenge to bring together such a wealth of expertise from countries all over the world, and to serve the entire community of Genitourinary/STI/Sexual Health physicians. We feel honored and are grateful to those experts, not only in WHO, CDC, and FHI, but also in many other institutions worldwide, who thought the project worthy of their support and contribution. The editorial team is grateful to Professor King Holmes for writing the Foreword for this edition.

We warmly thank the Authors and the Section Editors for their extraordinary dedication to a demanding time schedule that has allowed the timely publication of this edition. In addition to a thorough review by the Section Editors, many chapters have been read and critically analyzed and improved upon by other colleagues. We greatly appreciate and acknowledge the encouragement of all the friends, well-wishers, experts, critics, families and all.

We would also like to thank the Editorial team of Elsevier Health Sciences for their continued support, understanding and encouragement, and above all, their patience. In particular, Mr. Shravan Kumar, the Development Editor, Ms. Shabina Nasim (Managing Editor), and Ms. Richa Srivastava and Shrayosee Dutta (Copy Editors) all of whom helped to make the second edition so promptly available worldwide. We would also like to thank Ms. Deepti Talwar (Research Fellow) and Shashi Saldiwal (Medical Social Worker), who helped in the compilation of material.

We, the Editors and Section Editors, hope that the book will be of value to all those who are interested in the study of Sexually Transmitted Infections.

Happy reading!

**Somesh Gupta**  
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September 20, 2011



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# section i

## INTRODUCTION

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# Sexual Health: Expanding Our Frame for Action

Kevin A. Fenton

## Introduction

Sexually transmitted infections (STIs) are among the most commonly diagnosed and notifiable infectious diseases in many parts of the world, with more than 450 million new cases of curable STIs occurring in adults each year.<sup>1,2</sup> In 2005, the total number of new cases of the four curable STIs was estimated to be 448 million—101.5 million cases of chlamydia, 87.7 million cases of gonorrhea, 10.6 million cases of syphilis, and 248.5 million cases of trichomoniasis.<sup>3</sup> STIs constitute a huge health and economic burden, especially for developing countries, where they account for 17% of the economic losses caused by ill health.<sup>4</sup> The associated costs include direct costs, both medical and nonmedical, for care and materials, and indirect costs of time spent sick, when individuals are unable to engage in productive activities.<sup>5</sup> In the United States, STIs account for an estimated \$15.9 billion annually to the healthcare system.<sup>6</sup> However, treatment costs for STIs vary tremendously between countries and are influenced by a range of factors, including delivery by the public or private sector; economies of scale; economies of scope; prevalence and incidence; epidemic phase; transmission efficiency; resource combinations and input prices; incentives to providers for high quality and quantity of service delivery; and willingness to pay for treatment as a function of price, income, and distance.

STIs consistently rank among the top 10 reasons for healthcare visits in most developing countries and substantially drain national health budgets and household income. Care for the complications of untreated STIs accounts for a large proportion of tertiary healthcare costs in terms of screening and treatment of cervical cancer, management of liver disease, investigation of infertility, care for perinatal morbidity, childhood blindness, and chronic pelvic pain. Stigma and discrimination constitute an additional burden on people living with and affected by STI/HIV, and their effect is partly mediated through economic mechanisms (e.g.,

limitations on education, employment, and housing), which affect the household's ability to generate income or to use its income to secure improved quality of life. Clearly, STIs, including HIV infection, remain major global public health concerns.

Historical approaches to the prevention and control of these infectious diseases have largely centered around the principles of prompt diagnosis and treatment of infected individuals and their infected or exposed partners; community and risk-group education and awareness; effective program leadership and governance; and program integration and health systems strengthening.<sup>7</sup> However, despite the availability of effective clinical, behavioral, and community-level interventions,<sup>8</sup> we continue to wage a losing battle against STIs in many settings, and in some populations, previously controlled STI epidemics are now resurgent.<sup>9</sup> These challenges have led to calls for a strategic refocusing of global HIV/STI prevention priorities and efforts, accompanied by increases in program-relevant research that aim to bring to scale the most effective interventions; combine effective approaches for greater effect; and address both the individual and contextual determinants of these adverse health outcomes.<sup>10</sup>

It is within this context that recent discussions at national, regional, and global levels have focused on the benefits of incorporating the more holistic approach of sexual health to complement and enhance current prevention efforts. Sexual health has been defined by the World Health Organization as “*a state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity. Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence*.”<sup>11</sup> Sexual health has considerable potential as a framework to guide and support national efforts to control STIs, to reduce associated adverse health outcomes, and to promote prevention and wellness. This introductory chapter introduces the concept of sexual health as a broader, more holistic

framework for understanding both the multi-level determinants of STI epidemics, and for refocusing on prevention and control efforts. The chapter also explores some of the challenges and potential benefits of adopting this strategic framework, and highlights potential steps for future action.

## Determinants of Sexual Health

Sexuality is a fundamental aspect of human life, carrying the potential to create new life and fulfilling both personal and social needs.<sup>12</sup> However, many adverse health outcomes result from unhealthy or otherwise uninformed sexual behaviors and attitudes, including HIV and other sexually transmitted infections, unintended pregnancies, and coercive behavior. If health is more than the mere absence of disease, then current conceptual frameworks for describing the distribution and determinants of disease within a population (a dynamic interaction among the host, environment and treatment and care services) should be expanded since the fundamental determinants of health at the population level are patterns of exposure and the social and economic, as well as physical, environments.<sup>13–15</sup> Similarly, adopting a sexual health approach requires a more inclusive frame in which not only the characteristics of the infectious agent; the nature, form, and effectiveness of prevention, treatment, and care services; individual characteristics; patterns of sexual behavior; and the characteristics of sexual networks; but also the more distal social and cultural environment, including norms and values, are incorporated into our understanding of determinants and help to shape our intervention responses. To optimize the benefits of sexual health throughout the lifespan and to reduce the adverse consequences stemming from unhealthy sexual behaviors, intervention opportunities to improve sexual health should be considered at every level of society from individuals and sexual partnerships to communities and public infrastructure (including government).<sup>16</sup>

## Infectious Agents

A wide variety of microorganisms (bacteria, viruses, fungi, and protozoa) and a few ectoparasitic arthropods (*Pediculus pubis*, *Sarcoptes scabiei*) have evolved to depend, in whole or in part, upon the human genital tract and human sexual behavior for their survival.<sup>17</sup> Including HIV-1, more than 30 pathogenic sexually transmissible agents identified to date are responsible globally for an enormous degree of aggregate morbidity and mortality. The dynamic interaction between these agents, individual sexual behavior and networks, and health systems drives the observed patterns and distribution of disease in the population. Because sexual behavior is essential to preservation of the species and is driven by a highly developed neurochemical pleasure reward system, it offers both a reliable ecological niche for infectious agents and a daunting challenge to modern-day practitioners of medicine and public health who endeavor to treat and control them.<sup>17</sup>

The continued spread and evolution of these infectious agents greatly influence the patterns of disease transmission and, ultimately, sexual health. Of major concern is the emergence of

antimicrobial resistance of some of these agents and the growing number of restrictions on the range of available antimicrobial agents for treating these conditions.<sup>18,19</sup> Other changes may make the infectious agents more virulent or may change their clinical manifestations.<sup>17</sup> Finally, their impact is determined not only by their effect on the immediate genital environment, but also by their more widespread effects and complications, further driving up costs, and causing additional morbidity and mortality.<sup>20</sup>

## Individual Factors

Individual characteristics, including patterns of individual sexual risk behavior, remain major determinants of the risk of acquiring an STI and therefore of sexual health.<sup>21,22</sup> There are several biological factors that make it easier or more difficult for STI (including HIV) acquisition, including the presence of other STIs, tissue or membrane vulnerability, and viral load.<sup>23–25</sup> In addition, an individual's pattern of sexual behavior, including the number of partners, and the spacing and rate of partner change, and the types and frequency of sexual practices, greatly influence STI transmission risk.<sup>21</sup> Given the highly social nature of sexual partnerships, individual behavior takes place within the context of sexual partnerships and often of sexual networks (a set of people who are linked directly or indirectly through sexual contact).<sup>26,27</sup> The pattern of linkages can drastically influence such health outcomes in a population as the transmission of HIV and other STIs.<sup>28</sup> With regard to disease transmission, the important characteristics of a network are its size and its density or connectivity.<sup>29</sup> Because networks are dynamic, with new linkages forming and old ones dissolving, time and place are important dimensions of networks which may evolve rapidly, especially in an era in which the internet, travel, and migration all play important roles in disease transmission and in the creation and dissemination of sexual norms and social values.<sup>30–32</sup>

Other individual characteristics such as, educational attainment, occupation, income level, sex and race or ethnicity, and sexual orientation can influence a person's position in the social hierarchy and consequently can influence one's risk of acquiring HIV and STIs.<sup>33–35</sup> When we take a broader view of sexual health, we see that these individual-level factors may directly affect the probability both of one's being exposed to the infectious agent and to one's increased vulnerability of exposure to transmission networks. They also represent an opportunity for intervention. Traditional approaches to STI prevention have focused primarily on getting individuals screened, tested, and treated for STIs, but it is increasingly recognized that approaches must be tailored both to meet the specific characteristics of the individual and to ensure the acceptability and cultural competency of the intervention. From a practical standpoint, it is essential that STI care providers be familiar with locally prevalent sexual practices and that they be able to assess individual risk of infection for STI and for transmission to partners. It is important to know which sexual behaviors can transmit which specific agents and to avoid making assumptions about who is practicing what types of behaviors.

## PREVENTION, TREATMENT, AND CARE SERVICES

The earlier STIs can be diagnosed, the earlier they can be treated and further transmission interrupted. Therefore ready access to, and uptake of high-quality and effective care are essential components of effective STI control strategies. This requires at-risk or infected persons to have access to stable, simple, rapid, inexpensive, and accurate diagnostic tests; high-quality clinical services that allow easy, affordable, and stigma-free treatment; effective behavioral and biomedical interventions to arrest disease spread and reduce high-risk behaviors; trained, culturally competent healthcare workers to provide consistent service; and data and information systems that allow monitoring of progress, impact evaluation, and quality improvement.<sup>36</sup>

There continues to be major progress with new diagnostic tests for STIs, including newer-generation nucleic acid amplification tests and an expansion of novel point-of-care diagnostics.<sup>37,38</sup> New preventive vaccines provide mixed hope for viral STI control. An effective, inexpensive, safe vaccine against hepatitis B has been available worldwide for almost 40 years, yet elimination remains a question of time, public will, and priorities.<sup>39</sup> The availability of new human papillomavirus (HPV) preventive vaccine is encouraging, although the expense and limited availability globally will severely restrict its potential to make great inroads on disease incidence in resource-poor settings.<sup>40,41</sup> For herpes simplex virus 2 (HSV-2), except for partial protection of seronegative women provided by one vaccine candidate, controlled trials of several others have failed.<sup>42</sup> Efforts to develop vaccines to prevent HIV have been complicated, costly, and disappointing, and although work on HIV vaccine continues, it will likely be 5–10 years or more before an effective vaccine is marketed.<sup>43</sup> While there is not yet a cure for HIV infection, there are a growing number of treatments that can extend life expectancy for those who have access to them.<sup>44</sup>

Access to high-quality curative services remains a challenge around the world, and too many people with acute STIs, or living with HIV, do not have access to the medical care that they need. Furthermore, the recent global economic crisis has caused a number of countries to scale back or reduce funding for STI programs, further complicating access and impact. Waiting lists to gain access to clinical services and other limitations on life saving HIV medications are increasing concerns in developing and developed country settings.<sup>45–47</sup> Having an adequate and accessible health workforce is fundamental to an integrated health system and for providing essential health services in developing countries.<sup>48</sup> The severe shortage of healthcare workers in many developing countries constitutes a major threat to the performance of health systems and undermines the ability of these countries to achieve the Millennium Development Goals and other internationally agreed upon development priorities.<sup>49</sup> The situation is exacerbated by the emigration of highly educated and trained healthcare personnel from countries with health systems in crisis, further weakening the health systems in their countries of origin.<sup>50</sup>

Efforts to promote sexual health must therefore incorporate and engage the health system as a major determinant of health outcomes. In addition to the traditional approaches of diagnosing, treating, and reporting infections, the health system provides an opportunity for improving linkages through program collaboration, for strengthening holistic service provision through appropriate client-level service integration, and for facilitating seamless referrals to supportive services that address the wider determinants. Training of healthcare providers to manage STIs competently is critical, but so too is building the workforce capacity to understand, recognize, and manage the broader determinants of sexual ill health.

## SOCIAL CONTEXTS

The term “social context” refers to demographic, socioeconomic, macroeconomic, sociopolitical, and related features of the individual’s environment. Economic forces, demographic features, and other structural aspects of society outside the individual’s control play an important role in epidemiological factors and individual behaviors, including sexual behaviors, transmission of STIs, and other health outcomes.<sup>51,52</sup> Community attributes—including poverty, rates of substance abuse, sex roles, norms for sexual behavior, and prevalence of STIs—can increase the frequency of and risk associated with individual behaviors and can impede the ability of individuals to adopt preventive behaviors. These social determinants, which are complex and, integrated with overlapping social structures and economic systems, are linked to a lack of opportunity and to a lack of resources to protect, improve, and maintain health. Structural and societal factors such as social and physical environments, and availability, cost of, and access to health services, create pathways or barriers to good health. These factors are affected by the distribution of money, power, and other resources, all of which can be addressed through policy. Environmental factors, such as housing conditions, social networks, and social support also are key drivers for infection with HIV and other STIs.<sup>34</sup> Many have argued that a sustained and effective response to STIs and their adverse outcomes will be achieved only when we move beyond controlling disease on the individual level and address the root causes of disease, including the social and environmental determinants of health.<sup>53–56</sup> Adopting a sexual health framework provides an opportunity to look beyond simply managing disease outcomes to incorporating a more holistic approach to achieving health.

## Sexual Health: Challenges and Opportunities

Numerous countries now have experience with adopting or integrating a sexual health approach to enhance their HIV/STI prevention efforts.<sup>57–59</sup> While rigorous evaluations of this strategy remain to be undertaken, the literature suggests that there are likely to be both varied understandings of the utility of this approach, as well as challenges and benefits to implementation.<sup>60</sup> The highly stigmatized nature of STIs (including HIV infection), sexual behavior, and human sexuality in many societies often



complicates efforts to speak openly about these issues, or to broaden the conversation to include sexual health. In other settings, sexual health-related issues, including HIV stigma and criminalization, discrimination on the basis of sexual orientation, sexual violence, and reproductive health have come to be focal points for political, religious, or social debate. Misunderstanding or misinterpreting what is included in, or intended by, sexual health, and how it can be achieved, may also make providers, policy makers, and communities reluctant to adopt this approach. Questions about the role of the public sector in what is perceived by many as an intensely private matter further complicate the issue. While none of these challenges is insurmountable, the ability to promote sexual health effectively at local, state, national, and global levels requires a realistic assessment of the opportunities for change; identification of the challenges facing implementation; engagement and mobilization of a wide cross-section of partners; and a commitment to utilize long-term strategic approaches to achieve change.

Nevertheless, there are potential benefits and opportunities for adopting or integrating sexual health into current HIV/STI prevention efforts. Sexual health provides a holistic approach to addressing STIs and related conditions that may be more legitimately added to, or integrated into broader governmental initiatives aimed at promoting health and wellness.<sup>57–59</sup> Placing sexual health alongside mental or cardiovascular health may legitimize conversations on STIs, HIV and reproductive health in otherwise challenging contexts. Sexual health has already been included in national strategic approaches to address HIV/AIDS,<sup>57–59</sup> allowing for a broader discussion and integration of other STIs, sexual behaviors, and reproductive health issues and for addressing stigma related to these issues.

Incorporating a sexual health frame to complement existing vertical programs may allow those involved in HIV/STI control to move beyond the siloed nature of their efforts, and to engage a wider range of strategic partners in their efforts, including those in reproductive, adolescent, school health and mental health.<sup>61,62</sup> This may be especially useful for engaging constituencies who may consider disease-specific targeted approaches more sensitive or stigmatizing. For example, great strides are being made in engaging faith communities around HIV/AIDS and sexual health, and many of these communities recognize the intrinsic value of sexual health and the glaring and urgent health inequities.<sup>63,64</sup> Similarly, for social or economically marginalized groups, including migrants; for lesbian, gay, bisexual, and transgender (LGBT) communities; and for drug users, a focus on sexual health may provide a more empowering way to engage in and to support positive action for change by focusing on the social context that places them at risk, not solely on the individual risk behaviors and adverse health outcomes.<sup>65,66</sup>

Adopting a sexual health frame may also facilitate improved integration and synergy through promoting combined messages and services.<sup>67</sup> Collaboration across prevention programs and appropriate service integration at the client level has been identified as a key structural intervention to enhance HIV/STI prevention

and control efforts.<sup>68,69</sup> Similarly, there has been increasing interest to deliver and evaluate the quality and benefits of integrating health messages between and across health concerns, as well as evaluating the combined benefits of effective actions.<sup>70–72</sup> This integrated approach to messaging and to providing services may be facilitated through adopting the broader sexual health frame, and it remains an area for evaluation and research.

## Sexual Health: From Theory to Action

Incorporating and implementing sexual health as part of our targeted efforts to prevent, treat, and control STIs provides an opportunity to take a broader approach to prevention, one that acknowledges and incorporates external contexts and the wider determinants of adverse outcomes related to HIV and other STIs. However, change is challenging and will require a commitment to articulating the rationale for and vision of change; to building coalitions for change; to utilizing a strategic approach to implementation; and to assessing and evaluating progress. Key among these is the importance of national leadership in facilitating change, whether through supportive policies, adequate resourcing, providing infrastructure, or coordinating partnership efforts. Efforts to promote sexual health should incorporate proactive strategies to engage political and other influential leaders at the national, state, and local levels to commit to sustained action, and to ensure that supportive and culturally competent policies are instituted, based on the best available evidence. Implementing effective sexual health policies requires a supportive policy context. As sexual health programs are scaled up, the policy framework—laws, regulations, norms—have to be supportive for programs to succeed. Practitioners must commit to working with governmental and nongovernmental partners to identify and provide a supportive environment to implement evidence-based policies related to sexual health.

Implementing a robust sexual health approach will require investments to strengthen the prevention, treatment, and care infrastructure (public and private) needed to provide appropriate sexual health services that are adequately linked to allied and support services, and to provide a seamless interface for clients to address complex health and social needs. Governments will need to ensure that comprehensive sexual health services are available to the public, and that health professionals are trained to provide such services. Other key requirements include commitments to address sexual health across the lifespan and to understanding that age-appropriate needs exist at all levels; and that effective partnerships with communities, service providers and policy-makers will be required to achieve change and to maximize health impact.

Research, evaluation and surveillance are needed to support and optimize national sexual health efforts. Research is needed to develop and assess new prevention approaches that utilize a sexual health framework, and to assess the feasibility and acceptability of such a framework to clients and providers. Research is needed also to understand the best way of integrating related services and approaches and to understand better the benefits and potential

costs of such integration. Improved surveillance will be needed both to monitor individual health outcomes related to sexual health and to assess comorbidities by behavior, socioeconomic status and geographic clustering to better target prevention efforts. Ultimately, a sexual health approach will require the identification of more robust indicators of sexual health, including disease outcomes, risk behaviors, patterns of healthcare access, network characteristics, and societal norms, attitudes and policies. This will enable jurisdictions to both evaluate their health status and to define appropriate goals for optimal sexual health.

Finally, adopting a sexual health approach will require that new and dynamic partnerships be created, with a wider range of constituents outside of the traditional HIV/STI prevention and control field. These partnerships can reinforce the importance of individual and community responsibilities in achieving the goal of creating societies in which individuals, families and communities are encouraged to understand human sexuality and to cultivate sexual health and responsible sexual behavior. While each person is responsible for maintaining one's own sexual health and for protecting the sexual health of others, there are also important dimensions of community responsibility for sexual health in which the social environment provides freedom from sexual violence, coercion, exploitation and discrimination.<sup>73</sup> These multilayered determinants of sexual health suggest that corporations, nonprofit organizations, faith communities, schools and federal agencies must be included in the partnerships to improve sexual health, and that care must be taken to include a more diverse range of constituencies from across the political, religious and social spectra. These strategic partnerships are essential to the broad acceptance and overall effectiveness of a sexual health effort.

### Summary

The urgent, complex, and enduring nature of the global STI epidemics, including HIV infection, suggests that we should not continue doing the same things and expecting different outcomes. Recent additions of biomedical interventions to the prevention toolkit are encouraging, but it is not wise to think that we will ever be able either to treat or to vaccinate our way out of these epidemics entirely without addressing their root causes and social contexts. Rather, what will be required is a fundamental shift in how we conceptualize and speak about sexual behavior, human sexuality, and sexual health, and their importance in our everyday lives. Key to this will be building societies that are committed to the sexual health of all people, in which individuals understand and respect their own sexuality and that of others, and the individual and community responsibilities in achieving optimal sexual health as accepted as valid components of overall health and well-being.<sup>74</sup> This will go a long way towards addressing the stigma, the discrimination, the fear, and the silence that continue to hamper global prevention efforts, prevent national commitment to action, allow complacency within communities, and harm lives around the world.

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# Historical Aspects of Sexually Transmitted Infections

James S. Bingham

## 2

### Introduction

Sexually transmitted infections (STIs) have an interesting history and are believed to have existed since earliest times. Their transmission is related to human nature and frailties and they can have devastating effects on the body, on the mind and psyche, and on the ability to procreate. Perceptions about STIs have varied from one society to another and even today, for example, the industrialized world has a relatively enlightened approach to human immunodeficiency virus (HIV) infection, whereas some southern African countries have, at one point, virtually denied their existence.

The recent history of STIs mirrors, to a degree, the development of modern scientific medicine. The advent of microscopy in the late 19th century allowed the identification of the causative organism of gonorrhea and, in the early 20th century, the causative organisms of chancroid and syphilis were identified. The first serological test for any infection, the Wasserman reaction, helped to confirm the presence of syphilis and the first disease-specific modern treatment for an infection, arsphenamine, was developed for syphilis in 1909. Discovery of the bacteriostatic sulfonamides in 1937 by Domagk permitted the first effective treatment for gonorrhea but antimicrobial resistance soon occurred. With manufacture of penicillin, the first bactericidal antibiotic in 1943, both gonorrhea and syphilis became reliably treatable. Resistance to antibiotics, now perceived as a major threat with bacterial infections, has not spared *Neisseria gonorrhoeae* and chromosomal and plasmid-mediated resistance have been identified.

As the science of virology developed in the middle 20th century, other common STIs became more readily recognized, such as genital warts caused by strains of the human papillomavirus (HPV) and genital herpes caused by the herpes simplex virus (HSV). Indeed, the first reliable antiviral agent, acyclovir, was developed to treat genital and oral herpes simplex lesions in the early 1980s. Meanwhile, the science of immunology was developing in the latter half of the 20th century, retroviruses had just been discovered and, in 1983, HIV was identified as the cause of acquired immune deficiency syndrome (AIDS). The immunological basis of this most

devastating of STIs was elucidated and more is now known about HIV than any other virus.

### When did it All Begin?

The origins of the venereal (sexually transmitted) diseases are obscure. Medical and other historians have often suggested that well-known diseases such as syphilis, gonorrhea, chancroid, and lymphogranuloma venereum have existed since earliest times. This may, or may not, be true and some of these individuals may have drawn conclusions from ancient texts and manuscripts which may not be accurate. While the infections certainly exist in *Homo sapiens*, did they occur in the preceding species, *Homo erectus* prior to 150,000 BC? No one knows, but the French philosopher, Voltaire summed it up well when he declared in his *Dictionnaire philosophique* that *Venereal diseases are like the fine arts—it is pointless to ask who invented them*.

In examining the old literature, primary sources are not always available and translations are open to misinterpretation. Clinical observation may have been poor and genital infection was often viewed with distaste. The Chinese may have produced the first description of a sexual infection; Captain Dabry, a French naval officer, made a study of Chinese medical writings dating back to 2500 BC, publishing his findings in 1863.<sup>1</sup> He was able to describe a “corroding ulcer” of the genitals in men and women, which developed within a few days of sexual intercourse, followed by pharyngeal and anal ulceration. It is not possible to know if this might have been syphilis. In 1872, the George Ebers papyrus was revealed, dating back to 1550 BC.<sup>2</sup> It contains a reference to vulvovaginal inflammation which has been loosely ascribed to gonorrhea and it also refers to remedies for lice infestations. Recent studies on the bones of Egyptian mummies, dating from the pre-Dynastic to Byzantine eras have not shown any evidence of bony syphilis, however.

### BIBLICAL REFERENCES

The Christian *Old Testament* is littered with accounts of marital infidelity, prostitution, and descriptions of what might have been

venereal or STIs.<sup>3</sup> One passage, in *Deuteronomy* 28:27, that might refer to secondary syphilis reads as follows:

*The Lord will smite thee with the botch of Egypt, and with the emerods, and with the scab, and with the itch, whereof thou canst not be healed.*

In another passage, Psalms 38:5, 7:

*My wounds stink and are corrupt because of my foolishness ... for my loins are filled with a loathsome disease, and there is no soundness in my flesh.*

Some have suggested that this could represent syphilis but it could just as likely be representative of any other ulcerative condition. The biblical character, Job, was polysymptomatic: he had skin ulcers, loss of hair, foul breath, bone pains, loss of appetite, diarrhea, and fever but despite all this he lived into old age. It is likely that all of this is referring to religious progress rather than to venereal disease.

The other disease, apparently recognized from earliest times is gonorrhea. A widely quoted text from the *Old Testament* is the following from the *Book of Leviticus*, 15:2-12.

*When any man hath a running issue out of his flesh, because of his issue he is unclean. And this shall be his uncleanness in his issue: whether his flesh run with his issue, or his flesh be stopped from his issue, it is his uncleanness.*

It is believed that this passage refers to a discharging condition but the organ or part of the body affected is not specified. If it does mean a urethritis, it could just as easily be nongonococcal as gonococcal in origin. However, the fact that this was likely to be sexually acquired is clear because the text goes on to say ... *And the woman if she has an issue she too ... and she shall be put apart for seven days.*

In the *Book of Numbers* there is an account of the Israelites making war on the Midianites. They were successful and returned with 24,000 women. Moses was not pleased and ordered personal hygiene for every man; the participants were quarantined outside the camp and all the Midianite women *that have known man by lying with him ... to prevent a plague amongst the congregation* were slaughtered. Clearly, Moses understood the epidemiology and its origin in sexual intercourse and he probably recognized that the incubation period too. In a way, he may have been the first recorded contact tracer and was certainly effective!

## GREEK AND ROMAN REFERENCES

Hippocrates (460–377 BC) lived some two centuries after the book of *Deuteronomy* was written. He was an astute observer who was able to describe disorders of micturition, menstruation, and pregnancy. He also referred to *moist ulcers, particularly of the mouth and genitals*. In *De locis affectis* is the following short statement—*No disease has more varied symptoms than strangury. It is most commonly found in youths and old men. In the latter it is more rebellious, but nobody dies of it.* Some believe that this statement refers to gonorrhea but it seems more likely that it

could just as well be referring to cystitis or to urinary obstruction due to stricture, calculi, or prostatic enlargement. Nevertheless, Hippocrates was apparently in no doubt that strangury was the result of indulgence in the pleasures of Venus.

Other Greeks, such as Aristotle and Plato have mentioned gonorrhea in their writings and in Seneca's letters, we discover that Epicurus, the founder of Stoicism's rival philosophy, may have died of the disease. Apparently, at the age of 71 years he developed acute urinary retention and, despite spending the last 2 weeks of his life in a bath, he was unable to relieve himself. Of course, he may have had a renal stone or prostatic enlargement but some say that his death was due to gonorrhea, with the urinary retention presumably being attributed to urethral stricture.

The earliest Latin medical writer, Celsus (25 BC–50 AD) devoted a whole chapter of his *De medicina* to genital diseases. He certainly described ulceration of the glans penis complicating phimosis, retention of urine and its relief by catheterization. Indeed, he was the first person to describe this treatment. He also mentioned growths and gangrene of the penis and he discussed *profusio seminis* in the following words: *There is a fault in the genital region called the shedding of semen. It occurs without sexual desire or erotic dreams in such a way that in time the patient is consumed by wasting.*

Galen (130–200 AD), the "Prince of Physicians," was the most famous Greek physician after Hippocrates and his opinions dominated European medicine until the Renaissance. He certainly described penile ulcers and reported anogenital excrescences which were probably warts. In *De locis affectis* he was the first to use the word gonorrhea to describe a condition that appears to be similar to *profusio seminis*:

*Gonorrhoea is an unwanted excretion of semen which you may also call involuntary; or to be more precise you may say a persistent excretion of semen without erection of the penis.*

Vertue has suggested that these descriptions do not resemble the features of contagious gonococcal urethritis that we recognize today although, they could be representative of chronic nongonococcal urethritis, spermatorrhoea, or even prostatitis.<sup>4</sup> Likewise, Karl Sudhoff (1853–1938 AD) who was the first German professor of the *History of Medicine*, in Leipzig was not convinced that there was definite evidence that syphilis existed in Greek and Roman times and made the following statement ... *The literary proof that syphilis existed in Greece and Rome must, for the present at least, be considered a failure.*<sup>5</sup>

## ARABIC AND OTHER REFERENCES

Rome was sacked by the Barbarians in 410 AD and the European civilization descended into the Dark Ages. By 500 AD the western Empire had disappeared and many doctors fled to the eastern Empire, centered in Constantinople. The Graeco-Roman tradition was maintained but ideas stagnated in Byzantine medicine. If medicine was not flourishing in Byzantium it was active in Islam. Arabic culture reached its zenith in the 9th and 10th centuries in Baghdad which was a particular center for

mathematics and science. The ancient medical writings were translated into Arabic and the writings of Islamic physicians became the standard texts for the Western world. Again, they do not appear to have described a disease resembling syphilis but were almost certainly seeing patients with gonorrhea. The Persian, Rhazes (860–932 AD), gave a full account of urethral discharge and its treatment by irrigation. He appears to have been familiar with urethral stricture and emphasized the importance of catheterization if there was retention of urine. Ibn Sina (Avicenna; 980–1037 AD), a notable teacher, described the treatment of acute urethritis by irrigating the urethra through a silver syringe. He is said to have further enhanced treatment by inserting a louse, sometimes referred to as a bug or a flea, into the fossa navicularis in difficult cases.

Surprisingly, there is little to be gleaned from the Chinese, Japanese, Assyrian, or Hindu texts. In the 5th century, however, a Hindu physician, Sushruta, devoted a chapter in his *Diseases of the Urinary Passages* to dysuria but it would seem that he did not relate this to sexual acquisition. This is surprising as he was well-acquainted with the treatment of malaria, plague, tuberculosis, and smallpox. Other Hindu physicians certainly used urethral irrigations too. In the 9th century, a School of Medicine was founded at Salerno in southern Italy. Teaching there was based on the Graeco-Roman and Arabian principles, and particularly on the writings and thinking of Avicenna. Urination after intercourse to protect the urethra was one of the aphorisms of the day. In England, John of Arderne (1306–1390 AD) who had been a physician to Richard II, also mentioned urethral irrigation. This seems to have been a little more sophisticated as he advised ... *take the milk of a woman, a little sugar, oil of violets, and barley water and administer it with a syringe.*

## THE MIDDLE AGES (1000–1400 AD)

In the Middle Ages, gonorrhea was certainly described but also there were many references to genital ulceration. The Italian surgeon, Theodoric of Cervia (1205–1298 AD) wrote a description ... *of the corruptions that appear in men around the prepuce on account of coitus with an impure woman.* His contemporary William of Saliceto (1210–1280 AD) described ... *ulcers and pustules that arise because contact with impure women is followed by the retention of filth or venomous material between the glans and prepuce.* There are many such writings and the nature of what they were describing is unknown although the possible diagnosis might include chancroid, genital herpes, erosive balanitis, and phagedenic ulceration. John of Arderne described this as follows:

*The man's yard began to swell after coit, due to the falling of his own sperm, whereof he suffered great grievousness of burning and aching as men do when they are so hurt.*<sup>6</sup> He managed this condition by cutting away all the dead flesh with a razor and applying quicklime, apparently with success.

It is noticeable in all these writings that little attention is paid to the treatment of women with genital infections. This may be because they were not highly regarded in the community and

therefore, did not receive medical attention. Or, they may have been regarded as corrupt and promiscuous and therefore not deserving of attention. Anyway, by the time of the Renaissance, some doctors were certainly reluctant to treat anyone with venereal diseases, and in London, a regulation in 1430 was passed which excluded patients with venereal diseases from public hospitals.

## Syphilis and Gonorrhea

### SYPHILIS

Europe was shocked by the appearance of syphilis in 1493, believed to have been brought back to Europe, from the New World, by Columbus's sailors. By the following year there were cases across the continent but an epidemic arose in Naples where the French King, Charles VIII, was besieging the city assisted by mercenaries, including some from Spain. Naples was defended by King Alphonso II, also with the help of some Spanish mercenaries. Both armies had camp followers and the nature of warfare at the time allowed these people to pass from one camp to the other. Such was the level of debauchery and prostitution that, while Charles was at first successful in capturing the city, an Italian alliance was formed and this combined with an outbreak of the new disease, resulted in the lifting of the siege. The French called it the Italian disease and the Italians, the French disease. Charles discharged his soldiers who returned to their homes across Europe spreading the disease as they went. Charles, himself, died of it in 1497.

By 1495 it had reached France, Germany and Switzerland, England and Scotland by 1497, India in 1498, and China in 1505. It was, seemingly, a much more virulent disease than that which we recognize today and a stream of publications soon appeared, mainly from Italy and Spain. The most famous was the poem, *Syphilis sive Morbus Gallicus*, by Girolamo Fracastoro (1498–1553 AD) (Fig. 2.1), published in 1530, in which he gave a clinical description and then described treatment with mercury and guaiacum, a South American/Caribbean wood resin. He recounted the tale of a shepherd, Syphilus, who defended Apollo and was punished with a foul disease. It was translated into English verse by Nahum Tate in 1686 AD and the term syphilis was first used in an English medical text in 1717 AD when Daniel Turner published his book *Syphilis: a Practical Dissertation on the Venereal Diseases*.

There was little clinical advance in the 16th century although Fallopius described the indurated primary sore of syphilis and was able to differentiate between condylomata lata and condylomata acuminata (genital warts). In the 17th century cardiovascular syphilis was described (Lancisi and Hermann Boerhaave). The French physician Jean Astruc (1684–1766 AD) summarized the body of knowledge in *De Morbus venereis* (1736 AD) and took the view that syphilis had been introduced to Europe and beyond by Columbus's sailors upon their return from Hispaniola (Haiti). Lazar houses, or locks, had existed across Europe for the treatment of leprosy, which may have been confused with syphilis. The UK





**Fig. 2.1:** Girolamo Fracastoro (1498–1553 AD). *Source:* Wellcome trust photographic library (Reproduced with permission).

had numerous such institutions and most European cities had similar arrangements.

### WERE SYPHILIS AND GONORRHEA MANIFESTATIONS OF THE SAME DISEASE?

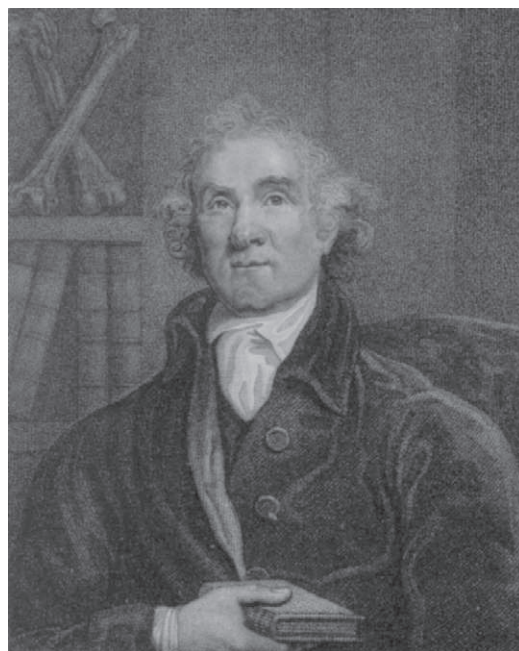
Early writers, such as de Vigo and Fernel, regarded syphilis and gonorrhea as different diseases but by the 16th century there was doubt about this. The Swiss physician, Paracelsus (1493–1541 AD), considered the two diseases to be one and the same and called syphilis “French gonorrhea.” Ambroise Paré (1510–1590 AD), the distinguished French surgeon and Thomas Sydenham (1624–1689 AD) as well as Jean Astruc believed that the two diseases were one and the same and were, therefore, regarded as *monists*.<sup>7</sup> By the mid 18th century some physicians were considering a separation between syphilis and gonorrhea once more. Hermann Boerhaave in his book on *lues venereal*<sup>8</sup> differentiated between the two diseases suggesting that gonorrhea was nothing more than a purulent catarrh, rather like that occurring with the common cold. There were other notable *dualists* such as Gerhard van Swieten (1700–1772 AD) in Austria.

John Hunter (1728–1793 AD) (Fig. 2.2), a Scottish surgeon practicing in London wrote a treatise on the *venereal disease* in 1786.<sup>9</sup> In this he made several major errors of interpretation. He believed that there was only one “venereal poison” and if this fell on a mucosal surface it would cause gonorrhea but if it fell on the skin it would cause a chancre and, if it was absorbed into the circulation it would cause constitutional syphilis. It was said that he carried out an experiment in 1767 in which he inoculated a recipient’s glans and prepuce with material from a patient with gonorrhea. Some said that the recipient was Hunter himself but

it is more likely that the subject of the experiment was a patient, reflecting the ethics of the day. A chancre appeared 10 days later with associated inguinal lymph gland enlargement, ulceration of the tonsils and a generalized skin rash. The whole illness lasted for some 3 years. Today, it has been interpreted that the donor had a double infection but the experiment convinced Hunter that he had been able to produce syphilis by the inoculation of gonorrheal pus.

Because of Hunter’s prestige, this view persisted until Benjamin Bell (1749–1805 AD), another Scottish surgeon based in Edinburgh, wrote his *Treatise on Gonorrhoea Virulenta and Lues Venerea* in 1793. In summary, he felt that the signs and symptoms of gonorrhea and syphilis were different. He said that gonorrhea did not progress to syphilis and that if they occurred together this could be explained by either having contracted both conditions at the same time or one after the other. He said that diseases in sex partners matched the diseases in index cases and, in Scotland, he said that he had never seen a patient with syphilis develop gonorrhea. Also, he noted that the treatment for syphilis with mercury was ineffective against gonorrhea.

Bell’s views were subsequently supported by the American-born Frenchman, Philippe Ricord (1800–1889 AD) (Fig. 2.3). He conducted a series of experiments where he inoculated pus from urethral discharge, genital ulcer or draining bubo into the patient’s own thigh and, covering it with a watch glass, examined the site daily for the development of lesions. He performed more than 2,500 of these inoculations and he published the results of his experiments in his *Traité pratique des Maladies Vénériennes*.<sup>10</sup> He concluded that an ulcerated chancre, or its resultant bubo, will always reproduce a chancre when reinoculated, that reinoculation of material from ulcers of secondary syphilis will not produce a



**Fig. 2.2:** John Hunter (1728–1793 AD). *Source:* Wellcome trust photographic library (Reproduced with permission).



**Fig. 2.3:** Philippe Ricord (1800–1889 AD). *Source:* Wellcome trust photographic library (Reproduced with permission).

chancere and reinoculation of the pus of blennorrhagia (gonorrhea) will not induce a chancre. Thus, he understood that syphilis had one cause and that gonorrhea was not caused by syphilis. He also thought that secondary syphilis was not contagious but this of course was a misinterpretation. While he maintained that view for many years, by 1858 he had to make a humiliating public announcement that he had been wrong.<sup>11</sup> Nevertheless, he proposed a simple scheme to classify syphilis, which was as follows:

- A primary lesion, a chancre, the first manifestation of an infection.
- Secondary lesions, resulting from that infection.
- Tertiary lesions (gummas) which rarely appear before the end of the 6 months but whose development could be delayed for many years.<sup>12</sup>

Experimentation continued and was not successful in lower animals. Eventually, primates were inoculated, and in particular the chimpanzee. One of the main researchers in this area was Albert Neisser who discovered the gonococcus in 1879. He found that monkeys did not thrive in Breslau, where he lived, and moved his laboratories to Batavia (now Jakarta) in Java. He stayed there for some years and produced the most comprehensive account of experimental syphilis ever published.<sup>13</sup> Within it he had established the incubation period of syphilis and confirmed the contagious nature of secondary syphilis.

## Identification of Causative Organisms of STIs and Confirmation of their Presence by Serological Means

### TRICHOMONAS VAGINALIS

There had been myths in the ancient world that human diseases might have been caused by small living creatures and this was

revived, as an idea, by Fracastoro in his *On Contagion*, in 1546. But with the advent of the microscope the French microscopist Alexandre Donné (1801–1878 AD), made a number of observations: he discovered platelets, noted the leukocytosis of leukemia and, in 1836, identified a flagellate protozoa, which was subsequently named *Trichomonas vaginalis*.<sup>14</sup> There was little interest in the organism, which was believed to be a harmless commensal. However, in 1894, *T. vaginalis* was found in the male urinary tract and it was suggested that it might be sexually transmissible. And it was not until the 1930s that the concept of sexual transmission became established.

### NEISSERIA GONORRHOEAE

As microscopy improved and because it was felt that gonorrhea might have a bacterial cause, effort was made to identify the causative organism. This was finally achieved in 1879 by Albert Ludwig Sigismund Neisser, working in Breslau which was then in Prussia but is now in Poland. He was using a Zeiss microscope with an oil immersion system and the new Abbe condenser. He was examining smears, stained with methyl violet by Koch's technique from 35 men and 9 women with purulent urethritis and 2 patients with acute ophthalmia. He was able to identify the small organisms as follows .... *They are seldom seen as solitary individuals; almost always they appear as micrococci packed close together so as to give the observer the impression of a single organism shaped like a figure of eight.* These, of course, were the gonococcal diplococci and Neisser's name was given to the genus. While he went on to culture the organisms on a meat extract-gelatin medium there is some doubt as to whether or not the organisms cultivated were actually gonococci. Attempts at inoculation did not produce clinical disease and so Koch's postulates were not satisfied. However, when the urethra of a man was inoculated in 1883 by Max Bockhart, classic gonorrhea developed after 3 days.

### TREPONEMA PALLIDUM

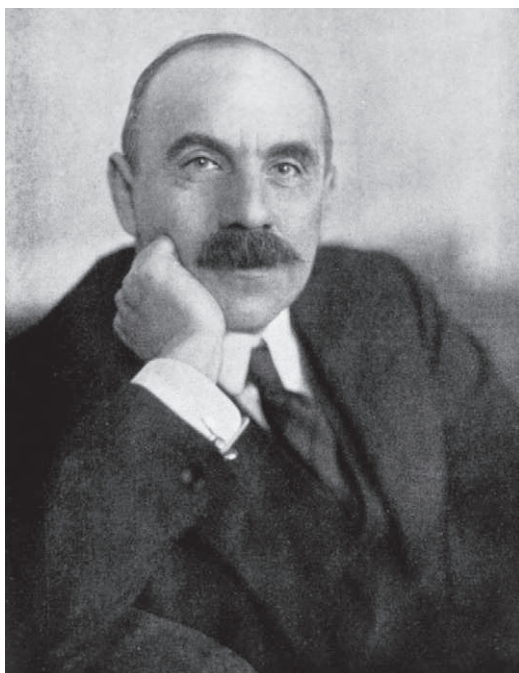
In 1905, at the Institute of Zoology, University of Berlin, an assistant claimed to have found a flagellate protozoon in syphilitic lesions. Other workers at the Institute treated this with some skepticism and it was decided to undertake further work which was entrusted to Fritz Schaudinn (1871–1906 AD) and Eric Hoffmann (1868–1959 AD). Using a Zeiss microscope with an apochromatic objective, Schaudinn examined a fresh preparation which Hoffmann had prepared from an eroded vulval papule in a woman with secondary syphilis. Several pale spiral organisms were seen which rotated about their long axis, and moved backwards and forward undergoing movements of flexion or angulation. They called the organism *Spirochaeta pallida* and subsequently found it in both fresh and Giemsa stained preparations from 11 patients with early syphilis. They were able to differentiate the pale finely coiled *Spirochaeta pallidum* and the dark, thicker *Spirochaeta refringens* which were often present in many nonsyphilitic specimens. A preliminary report was written up in April 1905.<sup>16</sup> Treponemes were identified



in the brain of patients with general paresis and tabes dorsalis by Hideyo Noguchi (1876–1928 AD), a Japanese pathologist working in New York. He was using tissue impregnated with silver nitrate.<sup>17</sup> For some years, a clinical resemblance had been noted between syphilis and yaws and, in 1905, Aldo Castellani (1877–1971 AD) working in Sri Lanka, found the spirochaete *Treponema pertenue* by microscopy of wet and stained specimens from patients with yaws.<sup>18</sup>

## Wassermann Reaction

The complement fixation reaction had been devised by Jules Bordet and Octave Gengou, working at the Pasteur Institute in Paris, in 1901. When Neisser returned from Java in 1906, he went to see his old friend August Paul von Wassermann (1896–1925 AD) (Fig. 2.4). They agreed that there was no satisfactory serological test for syphilis and they decided to apply the complement fixation technique to the disease. Neisser agreed to supply extracts of syphilitic organs from apes and humans to use as antigens and Wassermann was to undertake the laboratory work. In fact, he was assisted by Neisser's assistants, Schucht and Bruck. They made rapid progress and the first results were published in 1906.<sup>19</sup> Wassermann was fortunate that he published first since Laszlo Detre (1875–1939 AD), a Hungarian physician, had carried out similar work and published his results a few weeks later. The test was often abbreviated to the “WR” and because the complement fixation test was time consuming, a simpler flocculation test was devised, originally in 1921, by Reuben Kahn in America. By 1941 the serologically reactive substances, cardiolipin and



**Fig. 2.4:** August Paul von Wassermann (1896–1925 AD). Source: Wellcome trust photographic library (Reproduced with permission).

lecithin were isolated from the crude alcoholic extract of beef heart which had previously been used as the antigen. A more modern test that was developed using this substance became known as the Venereal Disease Research Laboratory (VDRL) test. Of course, it had been recognized from early experience that the WR could sometimes give false positive results in people without syphilis and it became clear that a specific serological test was required. The first of these to be introduced by Robert Nelson and Manfred Mayer at the Johns Hopkins School of Hygiene and Public Health in 1949 was the *Treponema pallidum* immobilization (TPI) test. Subsequent newer specific tests are well-known to current practicing physicians.

## CHANCROID

It had been recognized for a long time that not all genital ulceration was necessarily due to syphilis but even famous physicians, such as Ricord, failed to realize that chancroid was a specific cause of genital ulceration. This situation was rectified by one of Ricord's pupils, Léon Bassereau (1810–1887 AD). He recorded that indurated chancres were usually followed by constitutional symptoms and signs while nonindurated chancres were a purely local affliction. He then went on by means of “confrontation”—what we would call today contact tracing, to demonstrate that each of these lesions was associated with a similar lesion in the sex partners of the index case.<sup>20</sup> His theory was supported by Joseph Rollet (1824–1894 AD), another French syphilologist who accepted that some cases were hard to classify. Chancroidal ulceration was repeatedly reinoculable in the same individual whereas a syphilitic chancre was not. Of course, he said, a mixed chancre could exist due to simultaneous infection by the causative organisms of the two diseases. Ricord was finally convinced by this and supported the views of his young colleagues.

The organism causing chancroid was finally identified by Augusto Ducrey (1860–1940 AD) who was working in Naples when he made his discovery. He had noticed that microscopic examination of pus from chancroidal lesions showed many different microorganisms. He inoculated some of this material into each patient's own forearm and the resulting ulcer was reinoculated and by doing so he was able to passage the bacteria many times. This allowed the contaminants to die out and he was thus able to describe a short rod with rounded ends which later became known, after him, as *Haemophilus ducreyi*.<sup>21</sup>

## DONOVANOSIS

This type of anogenital ulceration, caused by bacteria to be identified was first described by Kenneth MacLeod (1844–1922 AD) who was working in the Indian Medical Service, in the days of the British Raj. His description of the condition was contained in a summary of the operations performed in his department in Calcutta during 1881.<sup>22</sup> It fell to an Irish colleague in the service, Charles Donovan (1863–1951 AD) to describe the causative organism. In 1905 he identified intracellular bodies which later became famous as “Donovan bodies” in stained tissue smears

from patients with donovanosis which he described under the heading *Ulcerating granuloma of the pudenda*.<sup>23</sup> Eventually, these were shown to be capsulated gram-negative bacteria but it was some years before it was possible to propagate them in the yolk sac of fertilized hens' eggs.

## CHLAMYDIAE

When Neisser went to Java in 1903 to study experimental syphilis in monkeys, he had among his team two young men, Ludwig Halberstaedter (1876–1949 AD) and Stanislaus von Prowazek (1875–1915 AD). While in Java they became interested in trachoma and, while Neisser forbade them from undertaking research on the disease, they went ahead and did it anyway and were able to identify inclusion bodies in conjunctival scrapings from orangutans which they had infected with scrapings from patients with trachoma. They published their work in 1907.<sup>24</sup> The findings were confirmed within a few years by other workers who reported similar inclusions in conjunctival cells from some infants with nongonococcal ophthalmia and in cervical cells from their mothers.<sup>25</sup> Halberstaedter and von Prowazek suggested the name Chlamydozoa for the organisms, derived from the Greek word *chlamys*, a cloak. They believed that they might be protozoa but when they found that they could not pass through bacteria-proof filters they regarded them as viruses, incorrectly as it turned out. A few years earlier, in 1904, Ludwig Waelsch in Prague described a form of nongonococcal urethritis which had an incubation period of some 10–14 days but ran a mild and protracted course. Some years later the urethroscopic features of this “Waelsch urethritis” was described as being similar to nodules in trachoma. Subsequently, in the 1960s, Moulder showed that chlamydiae are intracellular bacteria and he introduced the current classification of a family Chlamydiaceae and the genus *Chlamydia* with two species *C. psittaci* and *C. trachomatis*, the latter comprising ocular, genital and lymphogranuloma venereum strains.<sup>26</sup> With the development of yolk sac culture of *Chlamydia* in the 1950s, Dunlop and colleagues were able to demonstrate the presence of *Chlamydia* in nongonococcal genital infection.<sup>27</sup>

## VIRUSES

### Genital Herpes

While the term “herpes” has probably been used for a long time, Jean Astruc is usually given credit for the first full description which appeared in his *De Morbis Veneris*, published in 1736.<sup>28</sup> He mentioned the common sites affected and the small blisters. Subsequently, dermatologists classified vesicular rashes and included herpes within that classification. It was Jean Louis Alibert (1766–1837 AD) who first described the condition in women, as well as men thereby suggesting the possibility of sexual transmission.<sup>29</sup> The natural history of the condition was described by Francis Booth Greenough (1837–1904 AD) at the Harvard Medical School who had read a paper to the American Dermatologic Association in 1880 on herpes

progenitalis.<sup>30</sup> He said that the disease was not serious, that it had a tendency to relapse and produce mental anxiety. It was the German dermatologist Paul Gerson Unna (1850–1929 AD) who concluded that women were just as susceptible to herpes as men. Finally, the American virologist Ernest William Goodpasture (1886–1960 AD) established the principle of latency of the herpes viruses.<sup>31</sup>

### Genital Papillomavirus Infection

Penile and anal warts had been known from ancient times and are extensively mentioned in Greek and Roman writings. They were commonly referred to using the word *figus* (a fig) and the term *Condyloma acuminatum* began to be used towards the end of the 19th century. At first there were descriptions in men only but both John Hunter and Benjamin Bell described their presence on the vulva in females. Various organisms were spuriously identified in the lesions and they were thought to be related to skin warts. There was considerable controversy as to whether or not they could be sexually transmitted with the Frenchman Jourdan stating in 1826 that they could occur in both sex partners.<sup>32</sup> Despite considerable doubt by most observers, thereafter, by the 1920s and 30s many venereologists had concluded that genital warts were sexually transmitted. The fact that skin warts were caused by viruses had been demonstrated early in the 20th century when inoculation of cell-free filtrates of excised warts resulted in transmission of the disease. Subsequently prostitutes were persuaded to permit inoculation of the genital area and, in one disgraceful experiment, a virgin was inoculated. Nevertheless, many dermatologists refused to believe that genital warts were transmitted sexually but the matter was eventually resolved by Barrett and his colleagues in 1954. They were able to study a large number of soldiers returning from the Korean war who had developed genital warts. They had the opportunity to examine the wives, some of whom developed lesions after their husbands' return. The conclusion was that the condition was highly contagious and should be classed as a venereal disease.<sup>33</sup>

### Human Immunodeficiency Virus (HIV)

In June 1981, an alarming report appeared in the pages of the Morbidity and Mortality Weekly Report of the United States Centers for Disease Control in which were described five cases of *Pneumocystis carinii* pneumonia occurring in previously healthy men in the Los Angeles area.<sup>34</sup> In the succeeding months similar cases were reported from other cities including outbreaks of other immune deficiency associated conditions such as Kaposi's sarcoma, mucosal candidiasis, disseminated cytomegalovirus infection, and chronic HSV ulceration. There was evidence of T-lymphocyte dysfunction and, in particular, there was marked depletion of the CD4+ T-lymphocytes. The initial cases were occurring in homosexual men but soon other cases appeared in intravenous drug users and in Haitians.

Because of the practice of voodoo in that country the idea that the problem might be zoonosis was entertained. However,

retroviruses had been discovered some years earlier and one of them, feline leukemia virus was known to induce immune deficiency. Because of this, retrovirologists began to look for another member of the family and, in 1983 Luc Montagnier and his group in Paris managed to isolate a retrovirus from a lymph node which they called lymphadenopathy-associated virus (LAV).<sup>35</sup> This was somewhat ignored until the following year when another group, led by Robert Gallo at the National Cancer Institute in Bethesda (USA), confirmed the isolation and considerably expanded the evidence linking this retrovirus which they called the human T-lymphotropic virus type 3 to the immunodeficiency syndrome. The virus was subsequently renamed the human immunodeficiency virus type 1 (HIV-1) and in 1986, a second immunodeficiency virus (HIV-2) was isolated from West Africa.<sup>36</sup>

But when did the virus enter the human host? Possibly, more than a million years ago a chimpanzee was infected by viruses coming from two different monkey species. This resulted in a recombination event producing a virulent virus that wiped out 90% of the chimpanzee population over the next 100,000 years. It is estimated that around 1900, in Africa, the first transmission events of the virus to humans occurred; over the next 80 years the virus produced mini-epidemics that flared and faded until, in the late 1970s, the epidemic gained momentum and rapidly assumed the proportion of a pandemic, spreading around the sub-Saharan part of the continent and exiting Africa to affect other parts of the world.<sup>37</sup>

The arrival of this new viral infection has had a profound effect on modern life. First of all there was fear, stigmatization of homosexual men and realization that the virus could be transmitted in blood and its products, as well as in other tissues resulting in expensive law suits against some governments who may not have moved quickly enough to screen the blood supply. As an STI, it is found in the young predominantly and, in some countries, such as in many African states, the educated élite have been decimated with devastating potential effects on economies. An explosion of scientific endeavor has taken place and more is now known about HIV than any other virus. The pathogenesis has been considerably elucidated and new classes of cytokines discovered. Treatment has advanced by leaps and bounds and but little progress is being made in vaccine development.

Most professionals strongly advised against sexual promiscuity or, at the very least, advocated the use of barrier contraception, and some governments engaged in national awareness advertising. In some industrialized countries this has had the effect of reducing the incidence of STIs, particularly among high risk groups.<sup>38</sup> It was given further impetus when it was realized that other STIs could facilitate HIV transmission.<sup>39</sup> However, for ordinary practicing venereologists it has been a fascinating experience dealing with the complex medical problems that people with HIV infection present. Indeed, with its multisystem dysfunction, it has been viewed by some as the new syphilis. Indeed, Sir William Osler's old aphorism ... "He who knows syphilis knows medicine" could equally apply to HIV infection.

## Hepatitis B Virus

The hepatitis B virus was identified by David Dane at The Middlesex Hospital in London, in the early 1970s (the Dane particle). At about the same time, when the serology of hepatitis B was being unraveled, it was soon noticed that acute hepatitis B was occurring among sexual contacts of HbsAg carriers. While there was an increased prevalence among individuals attending STI clinics, the most striking serological evidence relating transmission of the virus to sexual practices was found in homosexual men having anal intercourse. Because of this risk, in industrialized countries, it is normal practice to offer hepatitis B vaccination to such individuals.

## ENTERIC BACTERIAL AND VIRAL INFECTIONS

The modern physician practicing in the field of STIs, in the industrialized world, is *au fait* with the infections particular to those using the anus as a sexual organ. Certainly, in the "Swinging Sixties" in London and elsewhere, 20% of gonorrhea and 70% of early syphilis was acquired homosexually. But it was soon realized, in the 1970s, that a number of enteric infections were more prevalent in this group too, transmitted by the feco-oral route through the practice of oro-anal contact—"rimming". These included *Salmonella*, *Shigella*, *Campylobacter* spp, as well as *Giardia lamblia*, *Entamoeba histolytica*, and hepatitis A,<sup>40</sup> sometimes collectively known as the "gay bowel syndrome."<sup>41</sup>

## Important Studies

It was realized that not all those infected with syphilis went on to develop the late forms of the disease. In order to determine more accurately what the spectrum of outcomes was, a prospective study was set up by the Norwegian syphilologist, Caesar Boeck (1845–1913 AD). He did so because he wondered if the patients would not do just as well if they did not have the unpleasant and somewhat ineffective treatments then available, mainly with mercury. He collected patients between 1891 and 1910 and his successor at the Oslo Dermatological Center, Bruusgaard, reassessed them in 1929 based on clinical examination and autopsy findings. The data were further analyzed by Gjestland in 1955.<sup>42</sup> The findings revealed that about a quarter of the untreated patients had at least one infectious relapse. Gummatous disease occurred in 15% of patients, usually within the first 15 years; cardiovascular disease developed in 14% of the men and 8% of the women, while neurosyphilis developed in 9% of the men and 5% of the women. Overall, 30% of the patients developed some type of late complication. This work is usually known as the Oslo Study.

More recently the US Public Health Service organized a study at Tuskegee, Alabama in 1932 and continued it for 40 years until 1972. All the patients were African-Americans and, while those with early syphilis were treated with arsenicals, the remainder were left untreated. The results of follow-up examinations were similar to those reported in the Oslo Study.<sup>43</sup> The study, by the



time it stopped in 1972, was considered as a national scandal as informed consent had not been obtained and the whole study was perceived as racist.<sup>44</sup> This work is generally referred to as the Tuskegee study.

After Tuskegee, one would have thought that such unethical research could never happen again. But some believe that it has with individuals in sub-Saharan Africa being tested, in large internationally sponsored studies, for HIV infection and not being informed of positive results, allowing unwitting transmission of infection to sexual partners and offspring.<sup>45</sup> And there has been a general reluctance to accept that unsafe medical injections could be responsible for a significant number of new infections.<sup>46</sup> There are a number of reasons for thinking this including that the HIV prevalence in children is too great to be explained by vertical transmission alone.

## Some Early Treatments

### SYPHILIS

There has been a huge variety of treatments recommended for syphilis prior to the advent of penicillin in 1943. Many were exceptionally unpleasant for the patient and, mostly, they did not affect a cure. Hilaire Belloc in his *Cautionary Tales* summed it up well:

*Physicians of the utmost fame  
Were called at once; but when they came  
They answered, as they took their fees,  
There is no cure for this disease.*

One of the first treatments was topical mercury, advocated by Celsus (25 BC–50 AD), the earliest Latin medical writer. He advised its use in new diseases as it had been useful in some skin conditions. Later, practitioners thought of it because of syphilitic skin eruptions often resembled other skin diseases. It was usually applied with a spatula, a process known as inunction. It might be continued for some 3–4 weeks. Unfortunately, there were many side effects, major among them being excess salivation and mucosal ulceration. This method was certainly used during the early European syphilis epidemic, as was also a wood extract from the West Indies (where the disease was said to have originated) – guaiacum.<sup>47</sup> This was probably no more than a sudorific and not as effective as mercury. Oral mercury was introduced by Philip Aureolus Bombastos von Hohenheim (1493–1541 AD), also known as Paracelsus (Fig. 2.5). The first preparation used was mercuric oxide—“red precipitate” or “angelical powder.” Later, metallic mercury was preferred – “blue mass” and this was the preparation used by Paracelsus. Other mercuric preparations were also used. Heat was thought to be an adjuvant to therapy and sweat rooms or bagnios were often employed. These preparations were difficult to take and a new form – the “blue pill” which was a mixture of mercury, confection of roses and powdered liquorice was used and there was even a preparation with brandy.

By the 19th century inunctions were revived in Vienna by Karl von Sigmund and later, in 1861, Ferdinand von Hebra, also



**Fig. 2.5:** Philip Aureolus Bombastos von Hohenheim, also known as Paracelsus (1493–1541 AD). *Source:* Welcome trust photographic library (Reproduced with permission).

in Vienna introduced mercury by injection. It was initially given intravenously but was later delivered by intramuscular injection. The timing and duration of treatment were discussed endlessly.

Iodides were first used in 1821 by Johann Christian Martini of Lübeck. However, the pharmacokinetics of this form of treatment were studied in Dublin by William Wallace<sup>48</sup> and they were used along with mercury and, in the 20th century, with arsenicals up until the advent of bismuth therapy in the 1920s. Of course, there was discussion about how these medications should be delivered, temporarily, and under the influence of Fournier in Paris, courses of mercury were used alternating with iodides for some 3–4 years and further courses could be extended twice a year until 10 years had elapsed. This was sometimes known as the Aachen treatment.<sup>49</sup>

In Germany, the distinguished researcher, Paul Ehrlich (1854–1915 AD) (Fig. 2.6) and his Japanese coworker Sahachiro Hata, were working on aniline dyes, particularly in relation to trypanosomiasis. They conducted a series of experiments and in experiment “606” the new substance arsphenamine or Salvarsan was identified. This was given intravenously and was found to be extremely effective in early infectious syphilis.<sup>50</sup> Originally, two or three injections were given with or without mercury and a number of trials were carried out by other workers including Albert Neisser. Ehrlich and Hata continued their experiments and in experiment “914” neosalvarsan was identified which could be given intramuscularly rather than intravenously. Newer arsenicals were subsequently introduced but had little real advantage over the originals.

In 1921, in Paris, Sazerac and Levaditi introduced bismuth.<sup>51</sup> This was given as intramuscular injections of sodium or potassium bismuth tartrate. It had an action intermediate between the arsenicals and mercury but, with its arrival, mercury therapy was abandoned and bismuth was given along with the arsenicals as



**Fig. 2.6:** Paul Ehrlich (1854–1915 AD). *Source:* Welcome trust photographic library (Reproduced with permission).

the treatment of choice. There were few side effects with this apart from blue discoloration of the gums.

However, while these treatments seemed to be helpful in early infectious syphilis they were not so effective against the late forms such as cardiovascular and neurosyphilis. Working in Vienna, the neurologist and psychiatrist Julius Wagner von Jauregg introduced fever therapy which he initially produced by using tuberculin and typhoid vaccine, particularly in cases of general paresis. In 1917, however, he introduced tertian malaria as a controllable source of fever with 10 febrile episodes being permitted before terminating them with quinine. This produced approximately a 50% improvement and von Jauregg was awarded the Nobel prize in 1927 for this advance.<sup>52</sup> In America, sophisticated “hot boxes” were invented, known as hypertherms, the most famous version being the Kettering hypertherm.

These treatments continued to be used until the early 1950s, along with penicillin.

In 1943, after penicillin had finally been manufactured through the work of Fleming, Florey and Chain, John Mahoney in New York in 1943, first used penicillin in the treatment of syphilis with dramatic effect,<sup>53</sup> and it has remained the treatment of choice ever since.

## GONORRHEA

An early treatment for urethral gonorrhea was a local astringent such as zinc sulfate. This was regarded as being somewhat irritating and silver nitrate, one of the new silver protein preparations was being used by the time of Neisser. However, urethral irrigations had been used since early times and irrigation with potassium permanganate was introduced by Weiss in 1880. This was the

solution used by most practitioners up until the advent of the antibiotic era. Irrigation apparatus became quite sophisticated and one version, designed by the American urologist Ferdinand Valentine, was used throughout the world for more than half a century.<sup>54</sup> The head of pressure advocated varied from physician to physician but too high a head often caused flushing of the infection higher up the urinary tract to the seminal vesicles, the prostate gland and the epididymis. Where urethral stricture occurred, usually in the posterior urethra, then urethral dilators could be used to relieve the stricture or sometimes gum elastic bougies could be used by the patients themselves. Progress with treatment was often assessed by urethroscopy and, in complicated cases, fever therapy was also used sometimes.

Gonococcal infection in the female was generally not so actively managed and was often left to run its course. Often complete resolution could occur but complicated gonorrhea with pelvic infection was a possible outcome. At one stage the vulva and vagina would be cleaned and the ducts of the accessory glands might be treated with a silver salt, mercurochrome, or acriflavine. Some practitioners irrigated the urethra with potassium permanganate and others cauterized the cervix with silver nitrate. Some even irrigated the uterine cavity through a cervical catheter and one can only imagine the consequences of such treatment.

Gonococcal vaccines were introduced at the time of the First World War and were generally reserved for the more complicated cases. Adequate treatment for gonorrhea did not emerge until Gerhard Domagk (1895–1964 AD) introduced sulfonamides in 1937.<sup>55</sup> Unfortunately, the gonococcus became resistant to this group of drugs very quickly and, by the time penicillin was introduced,<sup>56</sup> the use of sulfonamides had been virtually abandoned.

Of course in the 19th century, in many parts of the world, only a few had access to modern methods of treatment so, for instance in India, there was extensive use of Ayurvedic treatment with traditional medicines.

## Attempts at Control

The steps that Moses took to limit the spread of STIs, in Biblical times, have already been mentioned in this chapter, and are probably one of the earliest accounts of such activities. During the Middle Ages in Europe, efforts were made to limit the spread of venereal diseases. For instance, in the Borough of Southwark in London, brothel keepers were forbidden from keeping any woman believed to be infected<sup>57</sup> and in Edinburgh, in 1497, those with syphilis were compelled to go to an adjacent off-shore island, on pain of being branded on the cheek.<sup>58</sup>

## SOME EFFORTS IN THE UNITED KINGDOM

The incidence of these infections was particularly high in the military and probably interfered with their efficiency. While the French provided licensed brothels for their troops, where the prostitutes were examined regularly, this did not occur

in most other countries. Thus, politicians were tempted to enact legislation to subject prostitutes to compulsory medical examinations. In England, this legislation was in the form of a series of Contagious Diseases Acts in the 1860s. There was a public outcry from women's groups and, despite the contrary opinion of the medical profession, the Acts were repealed in the 1880s. Further, legislation in the form of the Notification of Diseases Act (1889) was passed, which allowed the authorities to impose restrictions on individuals suffering from certain infectious diseases. This time, the medical profession opposed including the venereologists among these as they thought that compulsory notification might lead to concealment of the infection, and thus defeat the object of the legislation. By the beginning of the 20th century in Europe, where there was some idea of the extent of the problem by the counting of cases, venereal diseases were considered to be a major health problem. In the United Kingdom, a Royal Commission was set up in 1913 to investigate and make recommendations. This it did in 1916, in the middle of the First World War. The report was extremely enlightening and proposed the provision by each local authority of a facility to treat venereal diseases, which was to be confidential, free and provided by doctors only, to prevent quacks for practicing in this arena. The Venereal Diseases Regulations were issued, based on this advice, in 1916 and have been continued in subsequent legislation ever since.

## THE FIRST WORLD WAR

During the First World War, the incidence of venereal diseases increased dramatically and soldiers, as they have always done, made liberal use of prostitutes. They were advised to wash the genitals with soap and water as soon as possible after intercourse and then irrigate the urethra with potassium permanganate solution (known by the troops as "*pinky panky*"). Thereafter, the advice was to apply calomel ointment to the whole area and a tube of argyrol to the urethra. This could all be accomplished in "*venereal ablution rooms*" provided by the Army. Eventually, at least for the British Forces, French brothels were placed out of bounds and a regulation was issued (no. 40D of the Defence of the Role Act) that made it a criminal offence for a woman with a venereal infection to solicit or have sex with any member of His Majesty's forces. This was bound to be largely ignored for obvious reasons.

When the United States entered the war in April 1917, the medical authorities in the US Army were keen to control venereal infections. They were impressed by the aggressive control policy of the New Zealand Expeditionary Force where there was a program of frequent medical examination of the soldiers for signs of infection, the issue of condoms and the provision of postcoital prophylaxis. Soldiers were required to attend prophylactic stations not more than 3 hours after exposure but, rather than have the prophylaxis administered by the soldiers themselves, as in the British Army, medical orderlies administered to the American soldiers. However, the US army was not banned from the French

*maisons tolérées* and the infection rates ran out of control to such an extent that in May 1918, an Anglo-American conference on venereal diseases was convened to discuss what measures might be necessary. The war ended before any significant progress was made. On the advice of Albert Neisser, the German Army was adopting similar programs.

## BETWEEN THE WARS IN THE USA

After the First World War there was a marked decline of interest in venereal diseases and, in the USA, federal control programs virtually ceased. While there was an alteration in the sexual mores of people, and sex before marriage was becoming more frequent, nevertheless the matter of venereal diseases was simply not discussed. Because of this, a determined young doctor, Thomas Parran (1892–1968) began to agitate. In 1926, he was appointed Chief of the Venereal Disease Division of the US Public Health Service and, despite the fact that funding became even more limited during the Great Depression, he nevertheless persisted in bringing the problem to national attention. He used the media, against considerable opposition, to do this and his book, *Shadow on the Land: Syphilis* was published in 1937 as a very considerable best seller.<sup>59</sup> He advocated mandatory syphilis serology before marriage and during pregnancy and by the mid 1930s this was largely established. Since he was an epidemiologist, his method of controlling syphilis was based on the case finding by the free provision of serology, prompt treatment and the tracing and examining of contacts. Eventually, in 1938, the National Venereal Disease Control Act was passed which authorized federal funding for a comprehensive control program.

## THE SECOND WORLD WAR AND AFTERMATH

Predictably, during the Second World War, the incidence of venereal diseases rose dramatically again. The role of prostitutes was not so great. Rather, sex did not always have to be paid for as a result of the changing mores of the time. The Japanese, on the other hand, forced women into prostitution as "comfort women", many of whom acquired STIs and both the Russians and the Japanese raped the conquered on a massive scale. The war was fought on a world-wide basis and some servicemen were seeking sex in parts of the world where the tropical venereal diseases were prevalent. In North Africa and in Italy, the problem became so great that the British and American allies decided to use the scarce supplies of penicillin rather than reserving its use for battle casualties alone, and the effect was dramatic. The Nazis regressed and began to include natural healing processes such as the use of leeches, bleeding and dietary measures.<sup>60</sup> In the post-war period with the arrival of penicillin and other antibiotics, it seemed as if it would be simple to control the venereal diseases. Indeed, the incidence of these infections declined markedly and they were perceived to be of much less public health importance than previously. As a result, particularly in America, a reduction in federal funding occurred and even great syphilologists, such as



Earle Moore, turned over his department to the study of chronic diseases at the Johns Hopkins Hospital in Baltimore.

In the United Kingdom, Ambrose King fought strenuously to maintain the nationwide system of clinics<sup>61</sup> and, fortunately, he was successful. Meanwhile, by the 1960s the incidence of STIs was increasing around the world and, particularly in the industrialized world the advent of the oral contraceptive pill, the abandonment of barrier contraception and alteration in the sexual mores mitigated for an expansion of the epidemic. More enlightened legislation changed attitudes to homosexuality and some male homosexuals adopted a lifestyle where anonymous sex with multiple partners, often unprotected, became the norm. This seemed safe enough to them as the bacterial infections, at least, could be easily cured. It all went horribly wrong in the late 1970s and early 1980s when HIV entered this community and spread rapidly. But it was not recognized at that stage that the infection was already well-established in sub-Saharan Africa and it spread with great velocity throughout the continent. Governments often ignored or even denied the situation and the HIV/AIDS epidemic is a human and economic disaster of monumental proportions. The World Health Organization (WHO) estimated, however, that the biggest epidemic would probably occur in the Indian subcontinent because of its social framework and vast population, and the government there was also slow to act. This has not yet been borne out. Infection rates are rising in China, the most populous nation on earth, and it is to be hoped that control measures may limit the spread in that country.

## THE WORLD HEALTH ORGANIZATION

The creation of WHO after the Second World War, with its division of STIs, has been a most beneficial development. It estimates the extent of the problem in countries and regions around the world and it provides technical assistance and training. It is recognized that in resource poor countries the luxury of a doctor-led case finding method of managing these infections is not the most practical approach. The notion of syndromic management has therefore been developed and algorithms of care, appropriate to a particular region, have been made available. This has been most useful in areas of high endemicity but the approach has often met with resistance from the local medical community. The WHO has developed management guidelines for syndromic approach and the antibiotics selected will be based on the known antibiotic resistance pattern (particularly for gonorrhea), in any area. Through its Gonococcal Resistance and Antimicrobial Susceptibility Project (GRASP) networks, it is able to monitor developments.

## Diagnostic Methods

For the most part of the last century, diagnosis of STIs has been made on clinical grounds, on the use of microscopy and culture (with antibiotic sensitivity testing) and on some serological testing (syphilis and HIV). The advent of nucleic acid amplification tests (NAATs) has changed that and some infections (*Chlamydia spp*) now are diagnosed predominantly using NAATs. It is possible to

multiplex these tests to identify more than one organism—tests for identification of *N. gonorrhoeae* and *C. trachomatis* are in widespread use already and soon multiplex tests for organisms causing syndromes such as urethral and vaginal discharge and genital ulceration will be available, identifying newly recognized organisms such as *Mycoplasma genitalium* as well. Recently, in Sweden, a NAAT test failed to identify *C. trachomatis* because the test target, the cryptic plasmid, had developed a 377 bp deletion in some cases, so constant vigilance is essential.<sup>62</sup> In London also, a NAAT test failed to diagnose infection with *C. trachomatis* because an organism had mutated to be plasmid-free, so, again, the target was not available. Rapid Point of Care Tests (POCTs) are being developed now, primarily for use in resource-poor parts of the world, although they will probably be used in the industrialized world as well (the plasmid-free organism<sup>63</sup> was suspected when a new POCT test was being compared with an established NAAT test and the former identified the infection and the latter did not). This is already happening with HIV testing, and to a lesser extent in the identification of syphilis, but availability of these tests and NAATs will enable nonspecialists to more easily make an accurate diagnosis.

## Vaccination

Prevention is always better than cure and, certainly through vaccination, some dangerous diseases have been eradicated (smallpox) and others massively reduced in incidence (polio, diphtheria, and childhood exanthemata). There has always been an aspiration to prevent STIs through vaccination but, until recently, this has been a vain hope. The big prize, of course, would be a vaccine against HIV with, currently, around an estimated 3 million deaths annually from HIV and AIDS and, by 2030, it is estimated that HIV will be one of the major causes of death worldwide, alongside heart disease and stroke. The problem is that ancestral viruses have been in existence for millennia and have learnt how to evade host immune responses. Add to that the extraordinarily rapid rate of mutation during replication and it is understandable that, so far, it has not been possible to produce an effective vaccine. There have been three large efficacy studies, all of which have failed to show any benefit. With the recognition that it will be some time, if ever, that a vaccine will be developed that produces a strong, effective neutralizing antibody response, researchers are looking at ways now to elicit effective T-cell responses against HIV. There may be much to learn from the long-term nonprogressor group, mucosal vaccines are being considered and there is on-going work in macaques to determine whether the protective potential of alloimmunity can be incorporated into effective vaccines against the simian immunodeficiency virus (SIV).<sup>64</sup>

Effective vaccines against hepatitis A and B have been available for some years, initial studies on new preventative and prophylactic herpes vaccines were unsuccessful in the 1990s, but there is hope that progress is being made and that successful vaccines may be in the pipeline. However, the one recent success has been the development and licensing of bivalent and quadrivalent HPV

vaccines. Industrialized countries are beginning to give these to early teenage girls to prevent the development of oncogenic HPV-driven cervical neoplasia.<sup>65</sup> This strategy is expected to be cost effective and, if it could be rolled out to resource-poor settings, might stop the untimely death of approximately 240,000 women from cervical cancer every year.<sup>66</sup>

## Conclusion

The terms STIs/venereal diseases have been used synonymously throughout this chapter and they have a fascinating history. Their incidence has waxed and waned down the centuries. New infections have been recognized, such as HIV infection, and while its incidence is still rising dramatically all over the world, huge scientific advances have taken place and are of advantage to medicine as a whole. The sexual mores of the world have changed dramatically over the past 100 years, many of the infections are now curable, new methods of diagnosis are available and the level of knowledge of the public has never been greater. Yet mankind has, apparently, not learnt much from all that has gone before and the prevalence of these infections is being maintained at a high level and is even rising. The war between disease and doctors, fought on the battleground of the flesh, may have a beginning, a middle but no end. Infections and epidemics arise within society and will remain a social product no less than the medicine, which opposes it. Civilization brings not just discontents but diseases too.<sup>67</sup>

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# section **ii**

## **EPIDEMIOLOGY** — *Christopher Fairley*

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# 3

## Global Epidemiology of Sexually Transmitted Infections\*

Ivonne Camaroni • Igor Toskin • Francis Ndowa  
• Antonio Carlos Gerbase

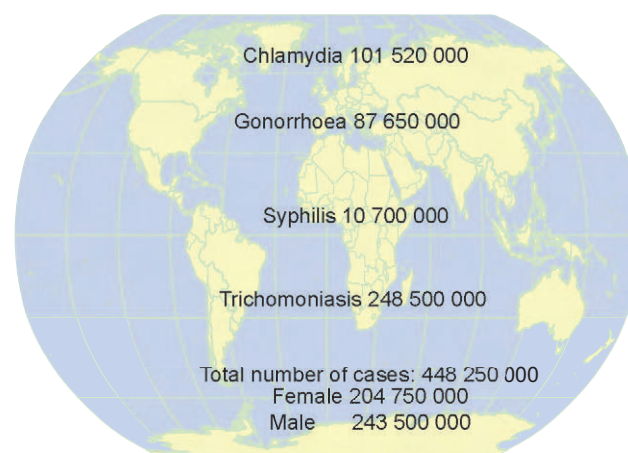
### Introduction

Sexually transmitted infections (STIs) represent a major public health problem. STIs are the cause of acute illness, long-term disability and death in women, men and infants, with tremendous economic consequences at individual and community level.

STIs were previously known as venereal diseases. Due to the stigma attached to this group of diseases, in the 70s the name was changed to sexually transmitted diseases. Recently, it has been discussed that 'disease' is not the most appropriate term to describe infections that may remain asymptomatic for many years or would never develop symptoms. Therefore, the World Health Organization (WHO) has recommended instead the use of sexually transmitted infections for the group of infectious diseases transmitted by sexual activity ([www.WHO.int](http://www.WHO.int)).<sup>1</sup>

In spite of available effective treatment for bacterial STIs, the incidence of STIs continues to escalate worldwide. WHO estimates that 480 million new cases of selected but curable STIs (Chlamydia, gonorrhea, syphilis, and trichomoniasis) occurred worldwide in 2005 (Fig. 3.1).<sup>2</sup>

Table 3.1 shows the breakdown of these infections according to WHO regions. WHO estimates are based on results from published and unpublished studies on prevalence of STIs and



**Fig. 3.1:** Estimated new cases of curable STIs among adults (WHO 2005).<sup>2</sup>

surveillance data. Data from different studies vary greatly in quality and accuracy and therefore the estimations should be taken with caution. Although aggregate data at national level may hide microepidemics in certain groups or geographic areas, the data are useful to analyze trends at national level.

**Table 3.1:** Estimated Incidence of Curable STIs by Region, (WHO 2005)<sup>2</sup>

WHO region	Chlamydia	<i>Neisseria gonorrhoeae</i>	Syphilis	<i>Trichomonas vaginalis</i>	Total
African region	10.0	17.5	3.4	78.8	109.70
Region of the Americas	22.4	9.5	2.4	54.9	89.20
Eastern Mediterranean region	5.7	6.5	0.6	12.60	25.40
European region	15.2	4.6	0.3	24.50	44.60
South-East Asia region	6.6	22.7	2.9	38.60	70.80
Western Pacific region	41.6	26.9	1.0	39.10	108.70
Global Total	101.5	87.7	10.6	248.5	448.40

\*This chapter is based on a WHO document "Prevalence and Incidence of Selected Sexually Transmitted Infections: *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, syphilis, and *Trichomonas vaginalis*: methods and results used by WHO to generate 2005 estimates" (WHO 2011, in press) developed by George Schmid and Julia Samuelson (WHO Staff members) and Jane Rowley (Independent consultant).

The burden of STIs is not only due to the acute episode of the infections, but it is determined also by the long-term and severe sequelae that many STIs may cause, such as infertility, ectopic pregnancy, and pelvic inflammatory disease.<sup>3</sup> It has been shown that both ulcerative and nonulcerative STIs enhance the transmission of human immunodeficiency virus.<sup>4</sup> In community trials conducted in Tanzania, the improvement in the management of STIs resulted in the reduction of the incidence of HIV by about 40%.<sup>5</sup>

Available data on prevalence and incidence of STIs is limited since STIs are usually not statutory notifiable. In many countries, therefore, the only data existing are from cross-sectional or point prevalence studies conducted among selected population. Many STIs are asymptomatic, or people are reluctant to seek healthcare due to the stigma attached to STIs. Consequently, in countries with STIs surveillance systems, the available data tend to underestimate actual prevalence and incidence rates.

Prevalence studies carried out in selected populations are not necessarily representative of the entire population. Pregnant women represent women of reproductive age who are fertile and seek prenatal care, but exclude single women, those who may have become subfertile or infertile due to a previous STI, and those with limited or without access to antenatal care services.

Accurate STIs prevalence data are needed in the planning, management, and evaluation of a control program. The importance of STIs as a public health problem needs to be estimated in order to advocate for sufficient resources allocation for their control and to assist decision-makers in defining and setting health priorities. Assessment of the magnitude of the problem posed by STIs should include a description of the incidence and prevalence of the diseases, characteristics of the affected population and any possible complications. Therefore, it is necessary to have a comprehensive and reliable surveillance system in order to know the distribution of STIs in the different age groups, sex, and geographical areas. A reliable system would enable follow-up of trends of STIs prevalence in the population.

## Surveillance of Sexually Transmitted Infections

Public health surveillance has been defined as: *the ongoing systematic collection, analysis, and interpretation of health data essential for planning, implementing, and evaluating public health activities.* Surveillance needs to be linked to timely dissemination of the data, so that effective action can be taken to prevent disease.<sup>6</sup>

The objectives of surveillance are to:

- monitor trends in diseases,
- identify problems that need intervention,
- improve effectiveness of prevention or healthcare resources,
- evaluate the impact of specific interventions.

According to the World Health Organization,<sup>7</sup> specific objectives of STIs surveillance are to:

- estimate the magnitude of the problem of STIs and improve program management;

- inform treatment recommendations and improve patient care.

There are four components of STIs surveillance needed in order to achieve effective control programs. These components are:

1. Case reporting.
2. Prevalence assessments.
3. Assessment of STI syndrome etiologies.
4. Antimicrobial resistance monitoring.

**Case reporting:** The report of cases of STIs by healthcare providers to public health authorities. Cases can be reported using an etiologic or syndromic diagnosis. Etiologic reporting is based on laboratory diagnosis, and therefore requires a well-developed laboratory system. Syndromic diagnosis may be used when access to laboratory services is limited. However, the specificity of this approach is lower than that of the etiologic diagnosis.<sup>8</sup> Case reporting can be conducted on a universal or sentinel basis depending on the national reporting system as well as on how services for the prevention and control of STIs are organized and delivered. Universal case reporting is the process where all healthcare facilities tally and report every case seen. Sentinel site case reporting is the collection of data from a select number of sites to capture health problems among “sentinel” populations thought to be representative of a population group of interest.

**Prevalence assessments and monitoring:** To regularly estimate prevalence of at least one STI and by doing so, monitor trends over time. Prevalence surveys are cross-sectional surveys that establish the frequency of disease and other factors in a community. They are useful to estimate the number of people in a population who have STIs and can also identify the differences in the frequency of infection in different population groups.

**Assessment of STI syndrome etiologies:** An important component of STI surveillance in countries with limited laboratory services. Periodic surveys provide information to keep guidelines for treatment of STIs updated.

**Antimicrobial resistance monitoring:** Due to the increasing rate of resistance of *Neisseria gonorrhoeae*, it is important to monitor antibiotic resistance in order to obtain current information for updating of treatment guidelines and to detect newly emerging resistance.

Surveillance systems should be evaluated periodically, *to promote the best use of public health resources by ensuring that problems of public health importance are under surveillance, that surveillance systems operate efficiently, and the information provided by surveillance systems is useful for public health practice. The evaluation should include recommendations for improving quality and efficiency.*<sup>9</sup>

It is very important to understand the magnitude of the problem posed by STIs in order to plan appropriate prevention campaigns, targeting key populations at higher risk of STIs. Studies evaluating the sensitivity of STIs surveillance systems are limited. In the Netherlands, the sensitivity of the statutory notification for gonorrhea has been estimated to be as low as 30%.<sup>10</sup>

Cultural values, myths, and beliefs are attached to sexual relations and therefore also attached to the infections. STIs are not merely a medical problem but a complex sociocultural and political problem. Cultural values and myths related with sexual issues contribute to the stigmatization of infections transmitted by sexual intercourse. Therefore, in order to achieve a sustainable reduction in the prevalence of STIs, a multidisciplinary approach is needed.

Effective treatment is an important component in the management of STIs, but alone it is not enough unless it coexists with public education and counseling. Strengthening of health services including laboratory facilities and mechanism for storage and distribution of drugs for treatment are essential steps in the management and control of STIs.

### Dynamics of the Transmission of STIs

The potential of an infectious disease to spread in a population or the rate of spread of one given disease is determined by:

**Contact pattern:** The rate of exposure of susceptible persons to infected individuals.

**Transmission probability:** The efficiency of transmission or the probability that a contact between an infected person and a susceptible one results in successful transmission of the pathogen so that the susceptible person becomes infected. The transmission probability depends on factors associated with the infected person, the susceptible contact, and the pathogen.

**Infectiousness:** The length of time an infected persons remains infectious, i.e., the period within the contact between an infected person and a susceptible one may result in the spread of the infection.

**Population immunity:** The proportion of individuals those are immune to the disease due to previous exposition to the pathogen or due to vaccination.

The rate of spread of STIs can be calculated using the reproductive rate of infection or average number of secondary cases of STIs resulting from a new case. The following model represents the reproductive rate of infection:  $R_0 = \beta \times c \times D$

In this model, ' $\beta$ ' represents the mean probability of transmission per exposure, ' $c$ ' is the mean rate of sexual partner change within the population, and ' $D$ ' is the mean duration of infectiousness of the newly infected persons.<sup>11</sup> If  $R_0$  remains less than 1, the infection eventually disappears from the population.

The transmission probability per partnership for *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Treponema pallidum* is estimated to be 0.5, 0.2, and 0.6 respectively<sup>12</sup> and the mean durations of infectiousness are presented in Tables 3.2 and 3.3.

The model used for the calculation of the rate of spread is a mathematical model that may contribute to the understanding of the 'dynamics of STIs.' However, the occurrence of STIs and their persistence in the population depend upon many complex factors related to both the individual and the community.

**Table 3.2:** Average Duration of Infection for Chlamydia and *Neisseria gonorrhoeae*<sup>2</sup>

Infection	Asymptomatic and not treated		Symptomatic and treated	
	Male	Female	Male	Female
<i>Chlamydia</i>	1.25 years	1.25 years	4 weeks	8 weeks
<i>Neisseria gonorrhoeae</i>	5 months	6 months	2 weeks	4 weeks

**Table 3.3:** Average Duration of Infection for Individuals with Syphilis Depending on Stage in which They are Treated<sup>2</sup>

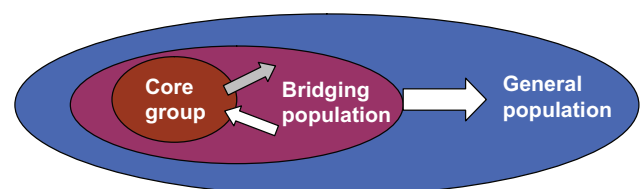
Primary	1 month
Secondary	3 months
Latent	3 years
Tertiary	15 years

Heterogeneity in contact rate, transmission probability, and duration of infectiousness produces different reproductive rates of the infection in different subgroups (Fig. 3.2).

The sexual contact pattern in a population is not a random mixing. Among people with high rate of concurrent sexual relationship the rate will be high, and therefore they may contribute to the persistence of infections through sexual route. Interaction within the subpopulation with high sexual activity, or core group, and the pattern of sexual contact between this group and the rest of the population is an important determinant of the spread of infection.

There are some characteristics of STIs that may contribute to the poor awareness of STIs in the population and consequently may slow down the progress of control programs:

- A high percentage of persons with STIs never present with symptoms and therefore, they are not aware of being infected or infectious. The decreased likelihood of seeking treatment results in higher percentage of undetected and untreated infections with risk for spreading and for complications.
- Complications after infection may develop many years after the acute episode. Due to the time lag between the acute episode of the infection and the development of sequelae, those at risk will not easily understand the relationship and consequently the need of behavioral change.
- Causative organisms change genetically, and therefore the development of effective treatments (drugs and vaccine) may be difficult.



**Fig. 3.2:** Dynamics of the STIs epidemic in the population.

- Microorganisms develop resistance against antibiotics, which contribute to treatment failure and prolongation of period of infectiousness.
- Due to the stigma attached to STIs, people are reluctant to seek care. In addition, health staff is not always prepared to talk about sexual issues with patients seeking care and therefore, the opportunity of tracing contacts may be missed. Both factors contribute to the persistence of infected people in the population.
- Many STIs induce limited or no acquired immunity, therefore individuals remain susceptible to reinfection.
- Lifelong persistence of virus such as HIV and herpes simplex virus contributes to life long infectiousness.

## Dynamics of the STIs Epidemic

There are many biological, cultural, and socioeconomic factors that contribute to the acquisition of an STI and hence to the perpetuation of the epidemic. Wasserheit<sup>13</sup> divides the underlying factors that contribute to the perpetuation of the epidemic into:

- (a) factors related to the microenvironment, i.e., those directly related to the individual;
- (b) factors related to the macroenvironment.

These two levels are closely related to each other: microenvironment could modify and be modified by macroenvironment (Table 3.4).

### MICROENVIRONMENTAL FACTORS

**Gender and age:** Cervical ectopy, which is frequently found in younger females, has been found to be a risk factor for acquisition of STIs. This is a factor that contributes to the increased vulnerability of younger women to STIs.<sup>14</sup>

**Age at first coitus:** Women with early sexual debut (10–14 year-old) have an increased risk of contracting STIs due to

immaturity of their reproductive tract and due to the increased number of years they will be exposed to STIs in comparison with those women who have their first sexual intercourse at adult age.<sup>15</sup>

**Anal sex:** Anal sex has been reported to be associated with self reported history of genital warts, genital herpes, and gonorrhea.<sup>16</sup>

**Sex during menstruation:** Tanfer et al.<sup>17</sup> found a strong association between sexual intercourse during menstruation and history of self reported STIs.

**Male circumcision:** Diseker and colleagues<sup>18</sup> have shown that the risk of contracting gonorrhea and syphilis is higher among uncircumcised men than among circumcised ones. No differences were found for chlamydia. A randomized controlled intervention trial conducted in a general population of South Africa has showed that male circumcision is associated with a protection of 60% (95% CI: 32–76%).<sup>19</sup> Trauma that the foreskin in uncircumcised men is exposed to during sexual intercourse, inflammation underneath the foreskin, and the high density of langerhans cells which are target cells for HIV are factors that may contribute to the increased risk for HIV in the uncircumcised.<sup>20</sup>

**Drugs and alcohol:** It has been suggested that alcohol consumption in conjunction with sexual activity may be related with impaired ability to practice safe sex.<sup>21,22</sup> Caetano et al.<sup>23</sup> found that people who had five or more drinks at one sitting have multiple sexual partners more frequently.

Epidemiological studies of the epidemic of syphilis in USA in the 1980s identified exposition to cocaine as a risk factor.<sup>24</sup> The use of cocaine may contribute to a decrease of inhibitions and an increase in sexuality. Men who have sex with men who use alcohol and drugs are at especially high risk for sexually transmitted infections.<sup>25</sup> It is not uncommon that drug users exchange sex for drugs and therefore they may have a higher number of sexual partners.<sup>26</sup>

### MACROENVIRONMENTAL FACTORS

**Poverty:** It may negatively influence the STIs epidemic by limiting the access to healthcare services leading to a delay in early diagnosis and treatment, or by limiting the access to education, which may decrease the accessibility to health information. In addition, poverty may result in increase in both male and female sex trade.

**Gender inequality:** In many countries, women are in a dependent situation, and therefore not able to negotiate issues related to their own sexual life including the use of condom.<sup>27</sup>

**Lack of openness to discuss sexual issues:** In many countries due to cultural or religious barriers, youngsters do not receive adequate information on sexual issues from adults but usually the only source of information are their peers. The information that the youngsters receive from their peers may be incomplete

**Table 3.4:** Determinants of STIs Epidemic

Microenvironment	Macroenvironment
<ul style="list-style-type: none"> <li>● Biological               <ul style="list-style-type: none"> <li>□ Gender</li> <li>□ Age</li> <li>□ Coexistence of other STIs</li> <li>□ Pregnancy</li> </ul> </li> <li>● Immunological</li> <li>● Behavioral               <ul style="list-style-type: none"> <li>□ Age at coital debut</li> <li>□ Multiple sexual partners</li> <li>□ Sexual practices:                   <ul style="list-style-type: none"> <li>— Anal sex</li> <li>— Sex during menstruation</li> </ul> </li> <li>□ Male circumcision</li> <li>□ Drug or alcohol use</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>● Cultural, social, and economic               <ul style="list-style-type: none"> <li>□ Poverty</li> <li>□ Gender inequality</li> <li>□ Health seeking behaviors</li> <li>□ Silent on sex issues</li> <li>□ Stigma and discrimination</li> </ul> </li> <li>● Epidemiological               <ul style="list-style-type: none"> <li>□ STIs prevalence</li> </ul> </li> <li>● Demographic               <ul style="list-style-type: none"> <li>□ Population age structure</li> <li>□ Sex ratio</li> </ul> </li> <li>● Political and structural</li> </ul>



or inaccurate and therefore it may not contribute towards safer sexual behavior.

**Stigma and discrimination:** Reaching key populations at higher risk of STIs particularly sex workers and men who have sex with men for services remains a challenge. Stigmatization and discriminations, especially in medical facilities, combined with restrictive laws are frequent obstacles to deliver STI prevention, treatment, and care services in these populations.

**Demographic factors:** In many developing countries, a high birth rate and short life expectancy determine a broad base pyramidal age structure, with a high percentage of the population within the reproductive age and therefore in the 'at risk' groups for STIs.

**Political and structural:** Lack of prioritization regarding STI program that is usually due to different competing public health issues that leads to a discrepancy between STI burden and resources allocated for the program.

## Chlamydia

*Chlamydia trachomatis* is the most common bacterial STIs in Western countries and an increasing public health problem in many developing countries. WHO estimates that 101.5 million new cases of chlamydia occurred worldwide in 2005 among those aged 15–49 years (Fig. 3.3).<sup>2</sup>

The information from developing countries is very scarce, partially due to the lack of cheap and reliable tests, which may hinder laboratory confirmation of suspected cases. Development of laboratory methods for detection of chlamydia infections

such as polymerase chain reaction (PCR), which do not require invasive procedures to obtain test samples, has facilitated both the diagnosis and screening activities in many countries. However, these tests are still very expensive and therefore of limited access in countries having inadequate resources. It is estimated that 85% of women and 40% of men are asymptomatic and therefore only detectable with screening programs.<sup>28</sup>

Chlamydia infections, if untreated, may persist for years. It is believed that spontaneous remissions may occur, but the rate for such remissions is not known. Studies on women with untreated chlamydia infections have shown culture positivity for more than 60 days; other studies have reported that infection may persist for years. In a review of the literature, Golden and colleagues<sup>29</sup> concluded that current data do not allow a reliable estimation of the duration of genital infection. It is uncertain whether immunity develops after exposure to chlamydia.

Chlamydia is less easily transmitted than gonorrhea.<sup>30</sup> In a study among patients with STIs and their sexual partners, a deterministic model was developed to calculate transmission possibilities.<sup>31</sup> It was estimated that transmission from men to women was 0.40 while for women to men it was 0.30. The study did not quantify the frequency of sexual intercourse and therefore the risk for transmission during a single sexual intercourse may be lower than observed in the study (Table 3.5).<sup>2</sup>

Stergachis and colleagues<sup>32</sup> found that some of the risk factors for acquisition of chlamydia among women are: age below 24-year-old, being single, having more than 2 sexual partners and practice of vaginal douching. Franceschi and colleagues investigated the prevalence of chlamydia on four continents and

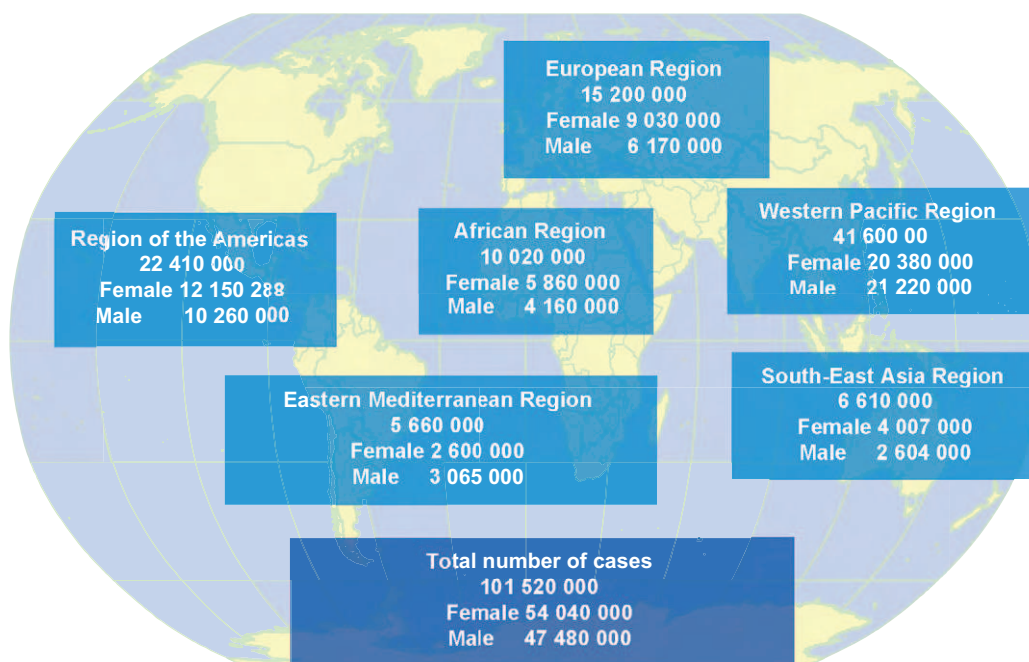


Fig. 3.3: Estimated new cases of genital chlamydia infections among adults (WHO 2005).<sup>2</sup>

**Table 3.5:** Estimated New Cases of Genital Chlamydia Infections (In Million) Among Adults, 2005<sup>2</sup>

WHO region	Incidence per 1000		New cases (in millions)		
	Females	Males	Females	Males	Total
African region	32.79	23.39	5.86	4.16	<b>10.02</b>
Region of the Americas	53.04	44.32	12.15	10.26	<b>22.41</b>
Eastern Mediterranean region	19.35	21.4	2.6	3.06	<b>5.66</b>
European region	39.89	27.06	9.03	6.17	<b>15.20</b>
South-East Asia region	9.2	5.63	4.01	2.6	<b>6.61</b>
Western Pacific region	43.31	42.7	20.38	21.22	<b>41.60</b>
<b>Global Total</b>	<b>32.22</b>	<b>27.32</b>	<b>54.04</b>	<b>47.48</b>	<b>101.52</b>

found that the chlamydia prevalence was greater in women aged 15–24 years than among those 25–44 years.<sup>33</sup>

Chlamydia infection during pregnancy may cause conjunctivitis or severe respiratory infections in the newborn. In a study conducted in Papua New Guinea it was shown that 57% of the conjunctivitis and 33% of cases of severe pneumonia in children under 3 months were due to *Chlamydia trachomatis*.<sup>34</sup>

Studies conducted among pregnant women have shown prevalence rates from 3% in Ghana to 29% in Fiji as shown in Table 3.6.<sup>35–43</sup>

Studies conducted among selected populations have shown prevalence of 41% among commercial sex workers in Indonesia (2000),<sup>44</sup> 32% in China (2001),<sup>45</sup> 25% in Bangladesh (2000),<sup>46</sup> and 5.8% in Canada (2001).<sup>47</sup> Prevalence of chlamydia among students and in the general population according to some studies are shown in Table 3.7.<sup>48–56</sup>

**Table 3.6:** Chlamydia Prevalence Studies Among Pregnant Women<sup>35–43</sup>

Country	Prevalence	Population	Reference
Botswana	8	13 ANC clinics	Romoren M et al., 2007 <sup>35</sup>
Brazil	9.4	ANC clinic - diverse demo and socio economic backgrounds, 11–47 years	Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Programa Nacional de DST e Aids, 2008 <sup>36</sup>
China	10.1	Pregnant women; 1st ANC visit	Chen XS et al., 2006 <sup>37</sup>
Fiji	29	ANC clinic attendees in Suva	Cliffe SJ et al., 2008 <sup>38</sup>
Ghana	3	Pregnant women attending ANC at Korle Bu teaching hospital	Apea-Kubi et al., 2004 <sup>39</sup>
Ireland	3.7	Pregnant women - asymptomatic, 15–50 years	McMillan et al., 2006 <sup>40</sup>
Japan	3.7	Pregnant women, 14–46 years	Shimano S et al., 2004 <sup>41</sup>
Lao	9.6	Pregnant women (<20 weeks) at first visit to Sethiathirath or MCH hospital	Thammalangsy S et al., 2006 <sup>42</sup>
Mozambique	4.1	Pregnant women attending antenatal clinic	Lujan et al., 2008 <sup>43</sup>

**Table 3.7:** Chlamydia Prevalence Studies in Different Populations<sup>48–56</sup>

Country	Prevalence	Studied population	Reference
France	1.6 female 1.4 male	General population, 18–44 years	ANRS. INED. INSERM. Quoted in ECDC Technical Report: Review of Chlamydia Control Activities in EU Countries, May 2008 <sup>48</sup>
Japan	6.8 female	Students from 9 schools (5 universities and 4 professional schools) located in the suburbs of Miyazaki City included students sexually active and not, 18–35 years	Imai H et al., 2004 <sup>49</sup>
South Korea	5 male	Sexually and not sexually active university students, 18–25 years	Lee SJ et al., 2005 <sup>50</sup>
Luxembourg	2.3 female 0.9 male	High school students, under 25 years	ECDC 2008. Technical Review of Chlamydia Activities in EU Countries <sup>51</sup>
Netherlands	2.5 female 1.5 male	General population, 15–29 years	Van Bergen J et al., 2005 <sup>52</sup>
New Zealand	2.7 female	University students, 18–25 years	Baker M et al., 2005 <sup>53</sup>
Norway	6.7 female 5.8 male	General population, 18–25 years	Steen et al., 2008 Referenced in ECDC <sup>54</sup>
Sweden	4.6 female 6 male	General population, 15–35 years	Novak DP & Karlsson RB, 2006 <sup>55</sup>
Thailand	7.5 female 6 male	Students at 2 vocational colleges, 15–21 years	Whitehead et al., 2008 <sup>56</sup>

## Gonorrhea

Gonorrhea is caused by *Neisseria gonorrhoeae* and transmitted almost exclusively by sexual contact or perinatally. The importance of gonorrhea is not only due to the acute symptoms that the infection causes but mainly due to the risk of complications and sequelae. If untreated, genital gonorrhea may lead to pelvic inflammatory disease in about 10–20% of women, a complication that may result in tubal occlusion and infertility. In men, untreated infections may result in epididymitis, prostatitis, and infertility.

Genital gonorrhea may be asymptomatic in both men and women, but it is more frequently silent in women: 30–80% of female cases of gonorrhea are asymptomatic in comparison with less than 5% of infected men.<sup>57</sup>

The risk of transmission of gonorrhea from an infected woman to her male partner has been estimated to be about 20% for a single intercourse, with a significant higher risk, about 60–80%, with more than four intercourses.<sup>58</sup>

The WHO estimates that gonorrhea accounted for 20% of the new cases of curable STIs worldwide in 2005, with 88 million new cases among adults aged 15–49 years (Fig. 3.4, Table 3.8).<sup>2</sup>

Between 1991 and 1996, a decline in number of gonorrhea cases was observed in many western European countries.<sup>59</sup> However, in early 2000 an increased incidence of gonorrhea has been reported in European countries.<sup>60,61</sup>

Gonorrhea is a common cause of urethral discharge, and it was found to be responsible for 69% of cases among men consulting due to urethral discharge in a clinic in the Central African Republic.<sup>62</sup> Prevalence rates in asymptomatic women in suburban community in Sudan were 1.2%.<sup>63</sup> Reported prevalence

**Table 3.8:** Estimated New Cases of Gonorrhea Infections in Adults, 2005<sup>2</sup>

WHO region	Incidence per 1000		New cases (in millions)		
	Females	Males	Females	Males	Total
African region	45.61	52.68	8.16	9.36	<b>17.52</b>
Region of the Americas	13.89	27.17	3.18	6.29	<b>9.47</b>
Eastern Mediterranean region	19.14	27.32	2.57	3.91	<b>6.48</b>
European region	10.71	9.72	2.42	2.22	<b>4.64</b>
South-East Asia region	16.32	33.61	7.11	15.55	<b>22.66</b>
Western Pacific region	35	20.94	16.47	10.41	<b>26.88</b>
<b>Global Total</b>	<b>23.8</b>	<b>27.47</b>	<b>39.91</b>	<b>47.74</b>	<b>87.65</b>

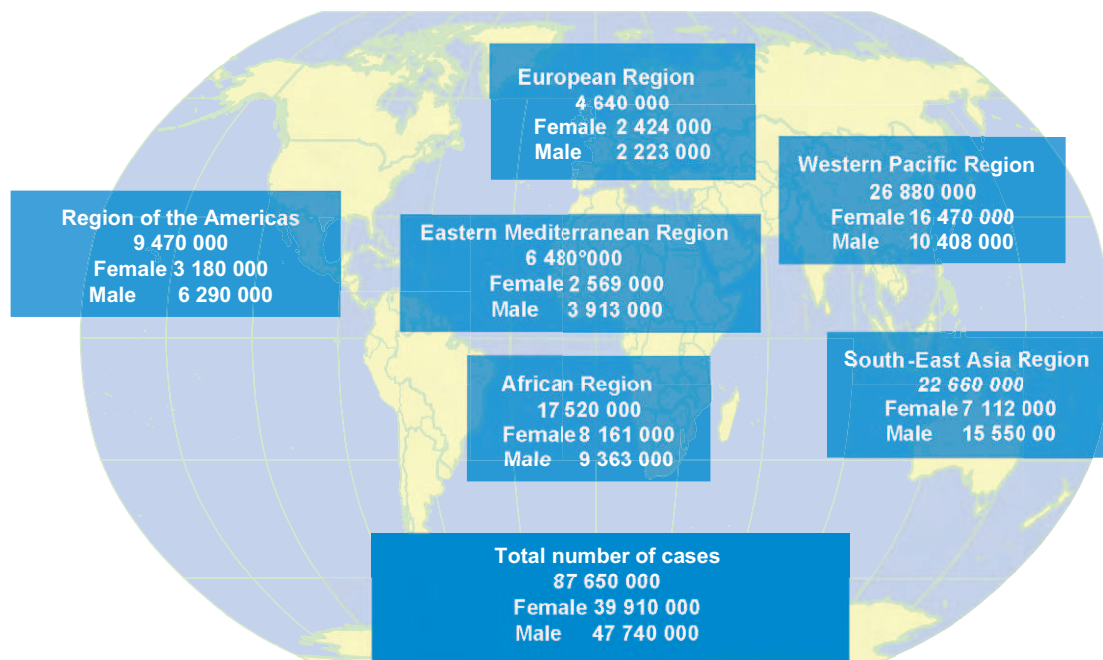
for adult male population was 0% in Japan,<sup>64</sup> 0.4% in India,<sup>65</sup> and 1% in Tanzania.<sup>66</sup>

Results of *Neisseria gonorrhoeae* prevalence studies conducted among pregnant women are presented in Table 3.9.<sup>35,37–39,42,43,67,68–72</sup>

## Syphilis

The prevalence of syphilis declined worldwide after the introduction of penicillin in the 1950s. In many Western countries, this trend was followed by an increase in the 1960s and 1970s probably due to the sexual liberation that took place during that period.

During the last decade, the prevalence of syphilis has decreased in many countries.<sup>73–76</sup> However, syphilis infection still is an



**Fig. 3.4:** Estimated new cases of genital gonorrhea among adults (WHO 2005).<sup>2</sup>



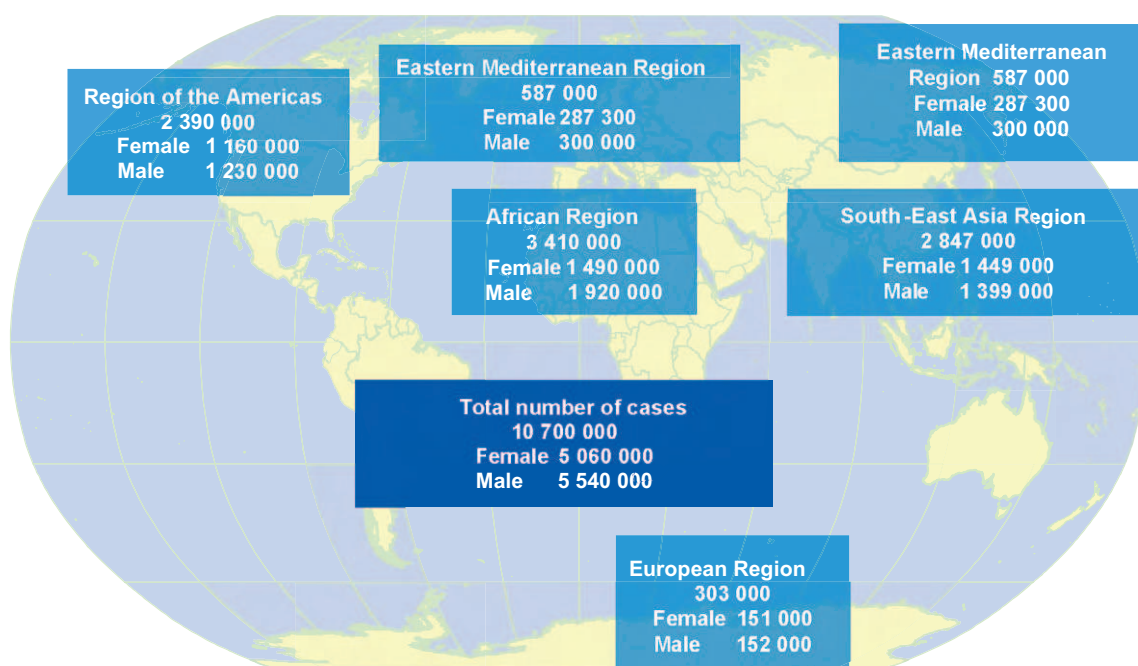
**Table 3.9:** *Neisseria gonorrhoeae* Prevalence Studies Among Pregnant Women<sup>35,37–39,42,43,67–72</sup>

Country	Prevalence	Studied population	Reference
Botswana	3	Pregnant women attending one of 13 ANC clinics	Romoren M et al., 2007 <sup>35</sup>
China	0.8	Pregnant women; 1st ANC visit	Chen XS et al., 2006 <sup>37</sup>
Democratic Republic of Congo	0.4	Pregnant women attending ANC clinic	Kinoshita-Moleka R et al., 2008 <sup>67</sup>
Fiji	1.7	ANC clinic attendees in Suva	Cliffe SJ et al., 2008 <sup>38</sup>
Ghana	0.6	Pregnant women attending ANC at Korle Bu teaching hospital	Apea-Kubi et al., 2004 <sup>39</sup>
Kenya	1.2	Pregnant women attending ANC clinic	Moses S, 2003 <sup>68</sup>
Lao	0.8	Pregnant women (<20 weeks) at first visit to Sethiathirath or MCH hospital	Thammalangsy S et al., 2006 <sup>42</sup>
Mongolia	6.1	10 randomly selected ANC clinicals	Report from MOH Mongolia, 2007 <sup>69</sup>
Mozambique	2.5	Pregnant women attending ANC clinic	Lujan et al., 2008 <sup>43</sup>
Nepal	2.3	Women who are 6 week postpartum with live birth residing in rural southeastern Nepal	Christian P et al., 2005 <sup>70</sup>
South Africa	8	Pregnant women attending ANC clinic	Sturm PDJ et al., 2004 <sup>71</sup>
Tonga	2.5	ANC clinic attendees attending central hospital	Cliffe SJ et al., 2008 <sup>38</sup>
Zimbabwe	1.1	Pregnant women attending ANC clinic	Mbizvo EM et al., 2001 <sup>72</sup>

important public health problem in many developing countries and a cause of increased concern in many countries in Eastern Europe and Asia.<sup>77–80</sup> In the newly independent states of the former Soviet Union, the rates of syphilis showed an increase of prevalence rates from 5.15/100,000 in 1990 to 120–170 per 100,000 in 1996.<sup>81</sup> A decrease or stabilization in same locations has been observed since 1997.<sup>82</sup>

WHO estimates that 10.6 million new cases of syphilis occurred worldwide in 2005 (Fig. 3.5 and Table 3.10).<sup>2</sup>

The risk of transmission from men to women is calculated to be less than 30%.<sup>83</sup> It has been well-documented that syphilis infection increases the risk of HIV transmission by at least 3-fold.<sup>84</sup> In addition, there is some evidence to suggest that syphilis infection may increase the HIV viral load of

**Fig. 3.5:** Estimated new cases of syphilis among adults (WHO 2005).<sup>2</sup>

**Table 3.10:** Estimated New Cases of Syphilis Among Adults, 2005<sup>2</sup>

WHO region	Incidence per 1000		New cases (in millions)		
	Females	Males	Females	Males	Total
African region	8.34	10.82	1.49	1.92	<b>3.41</b>
Region of the Americas	5.06	5.33	1.16	1.23	<b>2.39</b>
Eastern Mediterranean region	2.14	2.09	0.29	0.30	<b>0.59</b>
European region	0.68	0.68	0.15	0.15	<b>0.30</b>
South-East Asia region	3.33	3.02	1.45	1.40	<b>2.85</b>
Western Pacific region	1.1	1.07	0.52	0.53	<b>1.05</b>
<b>Global Total</b>	<b>3.02</b>	<b>3.19</b>	<b>5.06</b>	<b>5.54</b>	<b>10.7</b>

coinfected patients, and may increase the risk of mother-to-child transmission of HIV.<sup>85</sup>

In seroprevalence studies among African pregnant women prevalence rates have been found to be as low as 0% in Democratic Republic of Congo and up to 6.8% in Zambia as shown in Table 3.11.<sup>43,67,86–89</sup>

Population-based syphilis seroprevalence studies in rural area in Gambia showed rate of 2.3% in women,<sup>90</sup> DHS National Survey in Uganda showed 3.1% syphilis seroprevalence in men and 3.1% in women,<sup>91</sup> and 6.5% in women and 7.7% in men in Zambia.<sup>92</sup> Community-based survey in Madagascar showed prevalence of 11.8% in male population.<sup>93</sup>

Among patients with genital ulcer disease, syphilis was found to be responsible for 29% of cases in Madagascar,<sup>94</sup> 19% in Rwanda,<sup>95</sup> 12% in Uganda,<sup>96</sup> 10% in India,<sup>97</sup> and 3.4% in Singapore.<sup>98</sup>

## Chancroid

Chancroid, caused by *Haemophilus ducreyi*, is a common cause of genital ulcer in developing countries, particularly in sub-Saharan Africa. However, due to the absence of a cheap and reliable test, prevalence studies from resource poor countries are limited. The accuracy of clinical diagnosis may range from 33% to 80%, and it is related to the prevalence of chancroid in the population and the experience of the physician.<sup>99</sup> The sensitivity of culture may vary depending upon the culture media used and it is only about 75% at best.<sup>100</sup> Another diagnostic method that may be used is serological tests, with a sensitivity of 60–80% compared with culture. Serological tests, however, do not allow for differentiation between a recent and a past infection.<sup>101</sup> Newer methods as polymerase chain reaction (PCR) have a sensitivity of 95% but are expensive and require good laboratory set up.

Few cases were reported in USA between 1950 and 1980. An increasing number of cases were reported during the 1980s, peaking in 1987.<sup>102</sup> Since then, the prevalence of chancroid has decreased. However, outbreaks have been reported.<sup>103</sup> In a study of STD patients with ulcer from 10 cities, *H. ducreyi* was detected in ulcer specimens from patients from only 2 cities.<sup>104</sup>

Prevalence studies in Ethiopia showed a prevalence of 10% among pregnant women and 19.4% among women attending gynecological, obstetric, and family planning clinics.<sup>105</sup>

In a seroprevalence study conducted among rural population in Uganda, 1000 individuals between 15 and 54 years were tested within 2 years interval. The prevalence found was 9.8% for men and 7.3% for women, with an incidence rate per 1000 person years of 24.6 and 20.0 for men and women respectively.<sup>106</sup> Higher seroprevalence rates were found among selected population with 86% positive for IgG and 69% for IgA among commercial sex workers in Lagos, Nigeria,<sup>107</sup> 68% in migrant mine worker in South Africa,<sup>108</sup> and 26.5% in truck drivers in Kenya.<sup>109</sup>

In studies aimed to determine the etiology of genital ulcer disease, chancroid was found to be a relatively common cause.

**Table 3.11:** Syphilis Prevalence Rates Among Pregnant Women in Africa<sup>43,67,86–89</sup>

Country	Prevalence	Studied population	Reference
Democratic Republic of Congo	0	Pregnant women attending ANC clinic	Kinoshita-Moleka R et al., 2008 <sup>67</sup>
Mozambique	4.7	Pregnant women attending ANC clinic	Lujan et al., 2008 <sup>43</sup>
Nigeria	1.87	Pregnant women attending ANC clinic for first visit	Federal Ministry of Health, Nigeria: 2005 National HIV/Syphilis seroprevalence sentinel survey among pregnant women attending ANC clinics, April 2006 <sup>86</sup>
Tanzania	1.6	Women attending 1 of 6 ANC clinics, 15–49 years	Yahya-Malima et al., 2008 <sup>87</sup>
Uganda	1.6	Pregnant women attending booking visit at Entebbe district hospital, 15–40 years	Tann CJ et al., 2006 <sup>88</sup>
Zambia	6.8	Pregnant women attending ANC clinic, 14–44 years	Zambia antenatal clinic sentinel surveillance report: 1994–2004 (2005) <sup>89</sup>

Almost 52% of cases with genital ulcer in Bombay, India,<sup>110</sup> 26% of cases in Malawi,<sup>111</sup> 33% of cases of genital ulcer in Madagascar,<sup>94</sup> 23.7% in Jamaica,<sup>112</sup> and 23% in Pune, India were labelled to be due to chancroid.<sup>97</sup> Cases in the first two studies were culture positive and the remaining studies used PCR for diagnosis of chancroid.

O'Farrell et al.<sup>113,114</sup> found that in Durban, South Africa, 22% of the ulcers in men and 14% in women were due to *H. ducreyi*, while a more recent study found positive culture for *H. ducreyi* in 38.1% of cases with genital ulcer.<sup>100</sup>

## Lymphogranuloma Venereum

Caused by *Chlamydia trachomatis* (serovar L1, L2, and L3), lymphogranuloma venereum (LGV) is still endemic in parts of Africa, India, and Southeast Asia. The infection is more common in women than in men, probably due to asymptomatic and undiagnosed infections among men rather than a true lower prevalence. In a study among attendees to an urban STD clinic in Nigeria, lymphogranuloma venereum was the most common cause of genital ulcer among women.<sup>115</sup>

In studies to establish the etiology of genital ulcer diseases conducted in different countries, the percentage of ulcer due to lymphogranuloma venereum varied from 24% in Madagascar,<sup>116</sup> 7% in Lesotho,<sup>8</sup> 3.9% in Jamaica,<sup>117</sup> and 1–1.6% in Singapore.<sup>98</sup>

LGV was a rare condition in Western Europe and USA prior to 2003. Since this time different outbreaks of LGV proctitis have been reported in Europe, North America, and Australia among men who have sex with men: 244 cases by December

2005 in France, 232 cases by March 2007 in the Netherlands, 492 cases by April 2007 in UK, and 88 cases by September 2007 in Canada.<sup>118</sup> The majority of the reported cases were HIV infected MSM with higher risk sexual behavior such as unprotected anal sex, fisting, and sharing sex toys.

## Trichomonas

In spite of being one of the most common STIs available, accurate data on the prevalence of trichomoniasis is limited because few countries include this condition in the existing surveillance of STIs. The recent publication showed high prevalence of infection caused by *Trichomonas vaginalis* (TV), in male population.<sup>119,129</sup> According to some researchers the laboratory methods as microscopy and culture that have been mainly used for TV infection diagnosis before molecular methods were established led to some underestimation of infection particularly among men. The currently available newer generation diagnostics (e.g., LCR and PCR) that are more sensitive and specific can be therefore, used in order to determine the level of prevalence of TV infection, both symptomatic and asymptomatic, in male and female population.<sup>120</sup>

The infection with *Trichomonas vaginalis*, usually acquired via sexual contact, may be asymptomatic in up to 80% of the women with laboratory confirmed infections. Trichomonas infection is believed to facilitate the spread of HIV,<sup>121</sup> and infections of pregnant women have been associated with low birth weight infant and preterm delivery.<sup>122</sup>

The WHO estimates that 248.5 million new cases of TV infection occurred worldwide in 2005 (Fig. 3.6 and Table 3.12).<sup>2</sup>

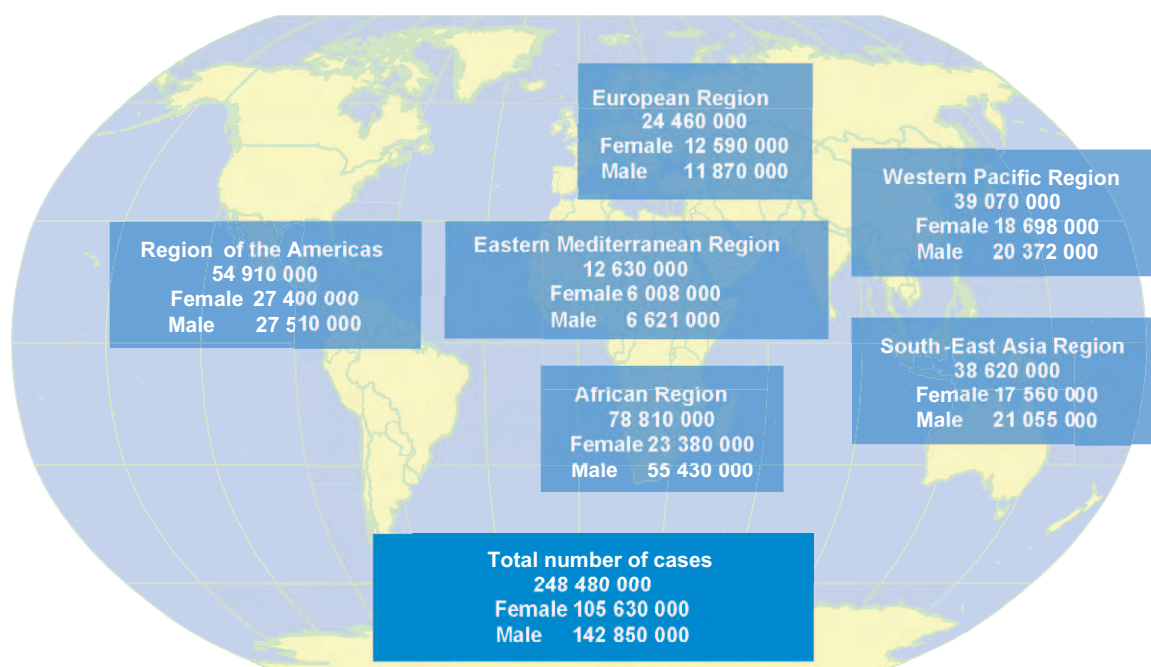


Fig. 3.6: Estimated new cases of trichomoniasis among adults (WHO 2005).<sup>2</sup>

**Table 3.12:** Estimated New Cases of Trichomoniasis Among Adults in 2005<sup>2</sup>

WHO region	Incidence per 1000		New cases (in millions)		
	Females	Males	Females	Males	Total
African region	130.74	311.83	23.38	55.43	<b>78.81</b>
Region of the Americas	119.55	118.83	27.4	27.51	<b>54.91</b>
Eastern Mediterranean region	44.76	46.23	6.01	6.62	<b>12.63</b>
European region	55.6	52.01	12.59	11.87	<b>24.46</b>
South-East Asia region	40.3	45.53	17.56	21.06	<b>38.62</b>
Western Pacific region	39.73	41	18.7	20.37	<b>39.07</b>
Global Total	62.98	82.21	105.63	142.85	248.48

**Table 3.13:** Trichomoniasis Prevalence Studies Among Pregnant Women<sup>37,42,69,129,13</sup>

Country	Prevalence	Studied population	Reference
Australia	7.2	Cohort of women attending aboriginal and islander health services in Townsville (provincial urban center)	Panaretto KS et al., 2006 <sup>129</sup>
China	3.2	Pregnant women; 1st ANC visit	Chen XS et al., 2006 <sup>37</sup>
Lao	1.8	Pregnant women (<20 weeks) at first visit to Sethiathirath or MCH hospital, population	Thammalangsy S et al., 2006 <sup>42</sup>
Mongolia	6.7	10 randomly selected ANC clinics	Report from MOH Mongolia, 2007 <sup>69</sup>
Samoa	20.8	Pregnant women; out of the women living in villages outside of Apia on the main island of Upolu (28, 68.2%), with the remainder living in Apia (132, 31.4%).	Sullivan EA et al., 2004 <sup>130</sup>

Prevalence studies in rural women showed prevalence rates of 2.8–5.1% in Thailand,<sup>123</sup> 15.1% in Bali,<sup>124</sup> 14–18% in South Africa,<sup>125,126</sup> 22.7% in Dar es Salaam, Tanzania,<sup>127</sup> and 23.8% in Uganda.<sup>128</sup> The prevalence rates of trichomoniasis among pregnant women in various countries are shown in Table 3.13<sup>37,42,69,129,130</sup>

*Trichomonas vaginalis* was found to be the etiological cause in 4.1–24.5% of men with urethral discharge in studies from Benin, Burkina Faso, Cote d'Ivoire, Ghana, Guinea, Mali, Senegal.<sup>131</sup> In Malawi, trichomonas was found in the urethra of 20.8% among symptomatic and 12.2% among asymptomatic men.<sup>132</sup>

## Herpes Simplex Virus

Herpes simplex virus 2 (HSV-2) is responsible for over two-third of all episodes of genital herpes and more than 5% of recurrent cases.<sup>133</sup> The majority of infections are unapparent or not recognized as genital herpes,<sup>134</sup> and consequently, estimation of the prevalence of herpes in the population, based on clinically apparent genital disease underestimates the true prevalence. Genital herpes infections are usually associated with an antibody response and therefore, seroprevalence studies are more accurate as an indicator for prevalence. Between 20% and 30% of young adults are seropositive for HSV-2.<sup>135</sup> HSV-2 seropositivity increases with age and it is correlated with socioeconomic status and number of sexual partners.

In studies conducted among sexual partners with discordant serology for herpes, it has been shown that the risk of contracting infection was about 10% per year, and the risk was higher for women (16.9) than for men (3.8). In women, the risk was lower for those who had HSV-1 antibodies. About 70% of the cases were acquired by sexual contacts that occurred during asymptomatic shedding.<sup>136,137</sup>

Genital herpes infection increases the risk of acquisition of HIV-1,<sup>138</sup> and the risk of spreading HIV infection due to high level of HIV-DNA in herpetic lesions.<sup>139</sup> It has been observed that the frequency of recurrent herpes infection in individuals who are HIV-1 positive is higher than for those who are HIV negative.<sup>140</sup>

Seroprevalence studies conducted among adolescents younger than 20-year-old have shown prevalence rates of 25–30% in Africa, 5–14% in USA, and 1.5% in European countries.<sup>141</sup> In USA, the prevalence of HSV-2 rose by 30% from 16.4% in 1976–1980 to 21.9% in 1988–1999.<sup>142</sup> In a literature review conducted by O'Farrell,<sup>143</sup> it was observed that herpes was one of the leading causes of genital ulceration in many countries and that the prevalence of herpes has increased between 1966 and 1999. In a study conducted among rural adults in Japan, the prevalence of HSV-2 decreased from 10.2% in 1973 to 1.2% in 1993.<sup>144</sup>

The WHO worked with colleagues at Imperial College, London, to model the estimated prevalence and incidence of HSV-2 infections. The total number of people aged 15–49 years who were living with HSV-2 infection worldwide in 2003 is estimated to be 536 million (Table 3.14) while the total number of people who were newly infected with HSV-2 in 2003 is estimated to be 23.6 million.<sup>145</sup>

Herpes virus infection is a common cause of consultation in STD clinics representing 24.6% of the total cases of STDs seen in clinics in Italy,<sup>146</sup> 25% in Spain,<sup>147</sup> 25.7% in New Zealand,<sup>148</sup> 32.3% in the Netherlands,<sup>149</sup> 42.9% in Tanzania,<sup>150</sup> overall prevalence of 55% in Paris with 67.3% and 44% among men and women, respectively,<sup>151</sup> and 64% in female STD attendees aged 18–35 in USA.<sup>152</sup>



**Table 3.14:** Regional Estimates of the Prevalence of the Herpes Simplex Virus Type 2 Infection Among Males and Females in 2003\*

Region	Regional prevalence in millions, by age															
	Female								Male							
	15–19 yr	20–24 yr	25–29 yr	30–34 yr	35–39 yr	40–44 yr	45–49 yr	Total	15–19 yr	20–24 yr	25–29 yr	30–34 yr	35–39 yr	40–44 yr	45–49 yr	Total
North America	0.9	1.5	2.0	2.6	3.2	3.8	3.9	17.9	0.6	1.0	1.4	1.7	2.2	2.5	2.6	11.9
Latin America and the Caribbean	2.6	4.5	5.8	6.4	6.7	6.6	6.0	38.6	0.9	1.6	2.1	2.4	2.7	2.8	2.7	15.1
North Africa and the Middle East	1.0	1.5	1.6	1.5	1.4	1.3	1.1	9.6	1.4	1.6	1.5	1.3	1.1	0.9	0.8	8.6
Sub-Saharan Africa	9.0	13.1	13.6	12.5	11.2	10.0	8.8	78.2	4.1	6.5	7.5	7.5	7.1	6.7	6.2	45.5
Western Europe	0.7	1.3	1.8	2.2	2.6	2.6	2.5	13.7	0.2	0.5	0.7	1.1	1.4	1.6	1.7	7.2
Eastern Europe and central Asia	2.7	3.9	4.3	4.3	4.3	4.7	4.7	28.9	0.6	1.1	1.5	1.8	2.1	2.6	2.8	12.3
Eastern Asia	2.6	4.4	7.1	11.1	12.8	11.9	12.0	61.8	2.0	3.4	5.4	8.4	9.8	9.3	9.5	47.8
Japan	0.4	0.6	0.7	0.7	0.6	0.6	0.6	4.1	0.02	0.05	0.08	0.1	0.1	0.1	0.2	0.7
Pacific	0.03	0.04	0.05	0.06	0.06	0.06	0.05	0.3	0.05	0.08	0.09	0.09	0.09	0.08	0.06	0.5
South Asia	4.1	5.4	5.5	5.4	4.9	4.3	3.7	33.2	1.8	3.1	4.0	4.8	5.2	5.4	5.2	29.4
South-East Asia	1.7	3.1	4.0	4.6	4.9	4.8	4.4	27.6	3.1	5.2	6.3	6.9	7.0	6.6	6.0	41.2
Australia and New Zealand	0.03	0.06	0.09	0.1	0.2	0.2	0.2	0.9	0.02	0.03	0.05	0.06	0.08	0.1	0.1	0.4
Total	25.8	39.4	46.5	51.5	52.9	50.8	47.9	314.8	14.6	24.1	30.5	36.1	38.8	38.8	37.8	220.7

\*Adapted from reference.<sup>145</sup>

Genital herpes is a common cause of genital ulcer in Africa. It was detected in 19% of cases with genital ulcer in Rwanda,<sup>95</sup> 42.5% in Nigeria,<sup>115</sup> 49% in Uganda,<sup>96</sup> and 35.8% in South Africa.<sup>153</sup>

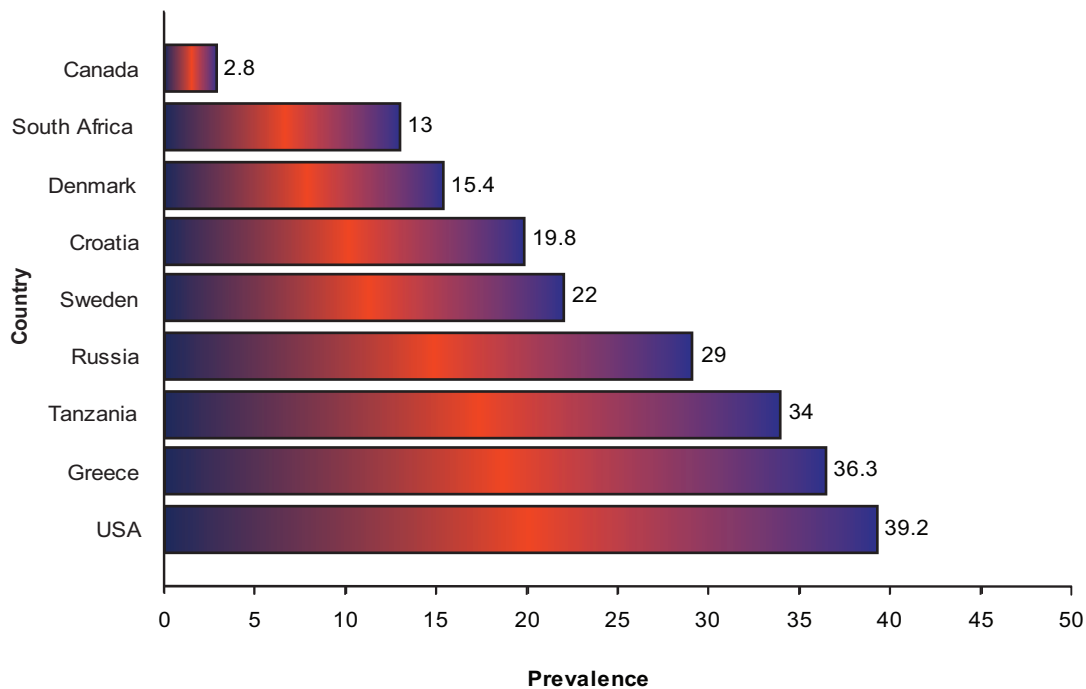
Similar studies in Singapore,<sup>98</sup> Jamaica,<sup>112</sup> and Madagascar<sup>94</sup> have showed a high frequency of herpes genital infection among cases with genital ulcer, 71.3%, 52%, and 10%, respectively.

### Human Papillomavirus Infection

There are more than 100 different genetic types of human papillomavirus (HPV) but it is the genotype 6 which is most commonly detected in genital warts. Infections with HPV are often subclinical or asymptomatic and an acute infection may be diagnosed only by the detection of HPV DNA in genital tract. Serological evidence of antibodies is sometimes the only indication of past exposition to the virus. Spontaneous regression of HPV infection was seen in 80% of women from a cohort study in Sweden, with a decline of the prevalence in the cohort from 21% to 8.3% during a 2-years interval.<sup>154</sup>

Seroprevalence in women without sexual experience is low. Prevalence rates increase to reach the highest percentage in sexually active young women to again decrease in older women.<sup>155</sup> However, in a population based study in Mexico for HPV seroprevalence, two peaks were detected, first in women in the age group under 25 years and the second in those aged 65 years and older.<sup>156</sup> In USA, it has been estimated that 1% of sexually active adults have genital warts, and that at least 15% have subclinical infection as detected by HPV-DNA assays.<sup>157</sup>

Figure 3.7 shows HPV prevalence rates obtained in studies conducted among asymptomatic students in Canada,<sup>158</sup> attendees to family planning clinics and private gynecological practices in South Africa,<sup>159</sup> healthy women aged 20- to 29-year-old in Denmark,<sup>160</sup> healthy sexually active women in Croatia<sup>161</sup> and Sweden,<sup>155</sup> attendees to gynecological clinics in Russia<sup>162</sup> and Greece,<sup>163</sup> pregnant women in Tanzania<sup>164</sup> and women aged 18–40 years in USA.<sup>165</sup>



**Fig. 3.7:** Human papilloma virus prevalence studies among female population.

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# Global Epidemiology of HIV Infection

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## 4

### Introduction

Human immunodeficiency virus (HIV) infections appear to be zoonoses derived from the chimpanzee (HIV-1)<sup>1,2</sup> and sooty mangabey monkey (HIV-2).<sup>3</sup> Only when these viruses are transferred to other primate species do they cause disease. In the case of HIV-1, the transfer to humans may have occurred as early as the 1930s.<sup>4</sup> The latter half of the 20th century then provided the social and economic conditions for the ensuing HIV pandemic, including:

- increasing urbanization, fostering prostitution,
- unprecedented travel and migration,
- wars,
- the emergence of injecting drug use (IDU),
- contaminated medical and other skin penetration procedures, and
- high rates of other sexually transmitted infections (STIs), particularly in the developing world.<sup>5–7</sup>

### Routes of Transmission

There are three major routes of HIV transmission: sexual, blood borne, and mother-to-child. The most common route of transmission of HIV is through unprotected sexual contact. Although sexual transmission accounts for about 85% of the global HIV burden,<sup>8–9</sup> the probability of infection through sexual contact appears to be lower than that of infection through other routes of transmission.<sup>10</sup> Transmission can occur when sexual secretions of an infected person come into contact with mucous membrane (oral, genital, or anal) of a noninfected person. The rate of transmission in receptive anal intercourse is much higher (1.7% per act) than vaginal intercourse. The female-to-male transmission rate is 0.04% per act and male-to-female transmission rate is 0.08% per act of vaginal intercourse in high-income countries. However, these rates are 4 to 10 times higher in low-income countries.<sup>11</sup> HIV transmission can also take place through oral sex, although the risk of transmission is too low to calculate.<sup>12</sup> Women are more susceptible to HIV infection than men<sup>13</sup> because of their physiology, vaginal ecology, and higher rate

of sexually transmitted infections (STIs).<sup>14–15</sup> HIV transmission through the sexual route is influenced by many factors, including the use of condoms, the presence of other STIs, male circumcision status, and viral load.<sup>8,16</sup>

HIV transmission also occurs parenterally through the transfer of contaminated blood, blood products, tissues, or organs. This route of transmission is important in IDUs, hemophiliacs, recipients of blood transfusions or organs, medical staff (doctors, nursing staff, and laboratory workers) that deal with infected materials, people who get tattoos and body piercings, and people that receive therapeutic injections in both formal and informal healthcare settings.

HIV can be transmitted from an infected mother to her child during pregnancy, during labor, and through breastfeeding. However, mother-to-child transmission (MTCT) can be reduced through improved health procedures (including caesarean section) and antiviral treatments and provision of formula milk.<sup>9,17–20</sup> The HIV epidemic in the heterosexual population can be assessed by routinely monitoring prevalence among pregnant women; this obviously also helps in preventing MTCT.<sup>21</sup> Probability of HIV transmission through various routes of infection has been listed in Box 4.1.

### HIV Surveillance

The ideal surveillance strategy would be to directly measure HIV incidence—the number of new HIV infections occurring each

#### Box 4.1 Ascending Probability of HIV Transmission Through Various Routes of Infection<sup>8,10,16</sup>

1. Blood transfusion
2. Transmission from mother-to-infant with perinatal zidovudine treatment
3. Transmission from mother-to-infant with perinatal zidovudine treatment
4. Needle sharing
5. Needle stick injury
6. Male-to-male sexual transmission
7. Male-to-female sexual transmission
8. Female-to-male sexual transmission



year. However, as this strategy would require massive population screening at regular intervals, no country has ever attempted it. Instead, countries have focused on measuring HIV prevalence and incidence in selected populations, either through repeat surveys or high levels of voluntary testing.<sup>22–24</sup> Different surveillance methods are discussed in detail in Chapter 6.

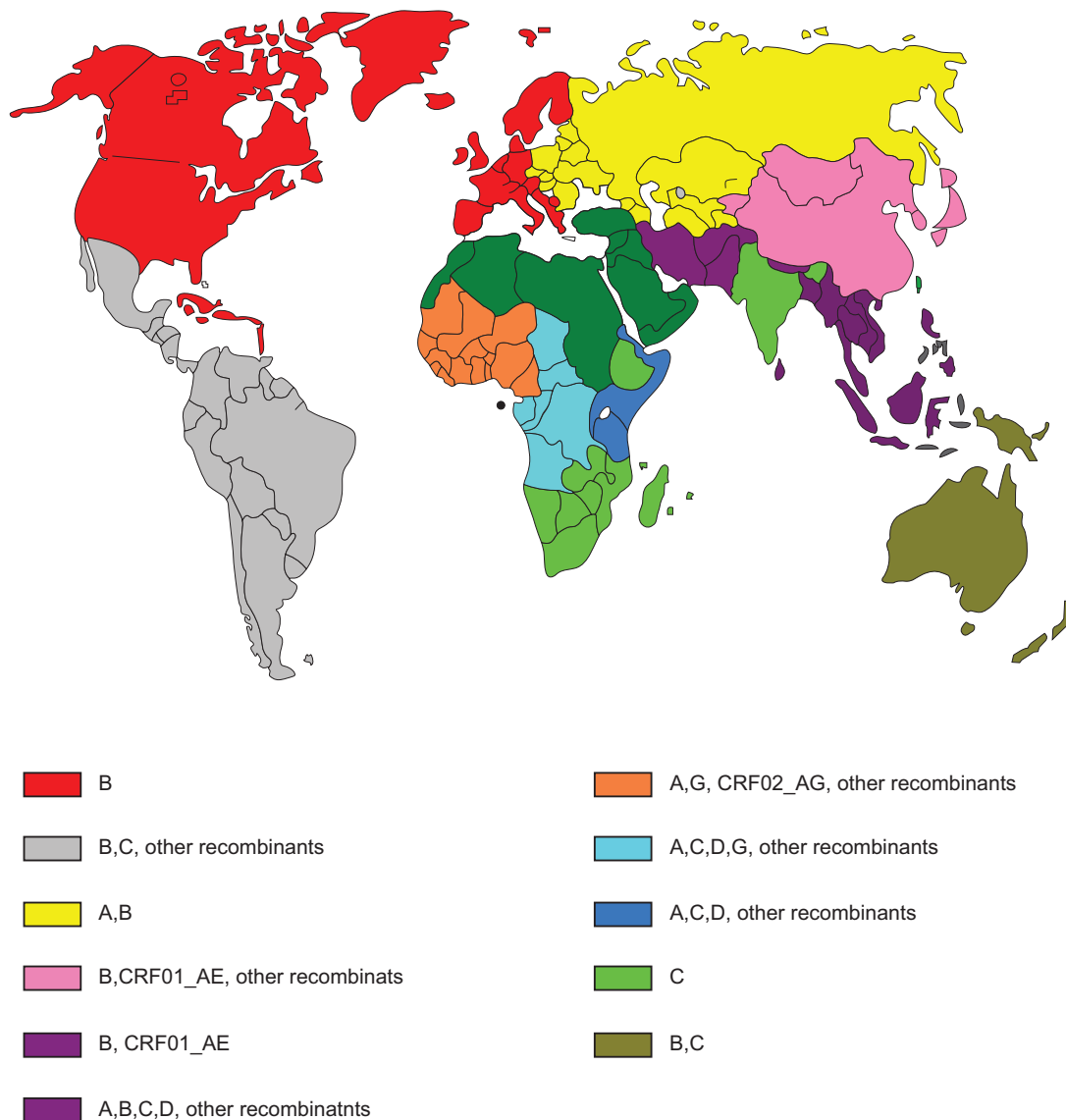
## Genetic Subtypes of HIV

Most HIV infections are caused by the type 1 virus (HIV-1), first identified in 1983.<sup>25–26</sup> HIV-2 was identified 2 years later in patients from Guinea Bissau and other West African countries, and is prevalent in those countries, also in Portugal and parts of India.<sup>27–31</sup> Infrequent cases with HIV-2 have been described in

western countries, such as Spain and France, and in Korea and Philippines.<sup>32–35</sup>

Three groups of HIV-1 (categorized as M, N, and O based on genome differences) have been described. Most infections with HIV-1 are caused by group M viruses that are divided into 9 subtypes (A–D, F–H and K). Subtypes are generally based on variations in RNA sequences that may differ between subtypes by up to 35%.<sup>36</sup> Globally, the prevalence of the different HIV-1 subtypes are diversely distributed (Fig. 4.1).

There are HIV-1 strains with genomes having RNA sequences from different subtypes (recombinants). Recombination occurs when two different HIV-1 subtypes co-infect a single cell and is generally seen in regions where more than 1 subtype is circulating. Recombinant variants that have been characterized



**Fig. 4.1:** Global distribution of HIV-1 subtypes and recombinants within each region in 2004. Subtypes and recombinants with >5% prevalence are shown for each region. Adapted from Hemelaar et al., 2006.<sup>36</sup>

by full genome sequencing and have been identified in at least three epidemiologically unlinked individuals are called circulating recombinant forms (CRFs). CRFs, such as CRF01\_AE and CRF02\_AG, play an important role in epidemics in some regions of the world, such as South and South-East Asia (Fig. 4.1).<sup>36</sup>

An understanding of the genetic characteristics of HIV strains can provide insight into the source of infection for an individual, and can also be applied at a population level to:

- suggest the external geographical origins of HIV isolates,
- determine clustering of subtypes, thus providing insight into the local HIV transmission dynamics,
- indicate the time that has elapsed since a subtype was introduced into a population; based on the assumption that the longer the subtype has been circulating in a population the greater its genetic diversity, and
- identify geographically appropriate vaccine candidates.<sup>37</sup>

The genetic diversity of HIV-1 could result in different biological properties, influencing transmissibility and pathogenicity of subtypes. However, proving this hypothesis has been challenging.<sup>36–37</sup>

## HIV in General Populations

### PREVALENCE ESTIMATION

The overall adult HIV prevalence in any country will generally lie somewhere between the prevalence found in blood donors (people with recognized risk factors are normally excluded from donating blood) and, say, sex workers (typically one of the first

affected populations).<sup>38–40</sup> However, the existence of paid blood donors in some countries can make this population unreliable as a lower limit.<sup>41–42</sup> Women attending antenatal clinics are regarded as providing one of the most reliable and accessible populations in which to measure HIV prevalence in the general sexually active population as they are not attending the service because of illness and because HIV infection does not substantially affect fertility. Nevertheless, a degree of selection bias is inevitable with any surveyed population. The more populations surveyed from a diversity of locations the more reliable the epidemiological picture.<sup>39,41</sup>

### GENERAL POPULATION INDICATORS OF HIV

Since 2000, the global prevalence of adults living with HIV has stabilized at 0.8%.<sup>43</sup> However, the estimated overall number of people living with HIV has increased from 29.5 million in 2001 to 33.4 million in 2008.<sup>43</sup> The increase in people living with HIV is attributed to new infections that continue to occur and the prevention of death due to improved accessibility to antiretroviral treatment.<sup>44</sup> An estimated 2.7 million new HIV infections (2.3 million adults and 0.4 million children below 15 years) and 2 million (1.7 million adults and 0.3 million children below 15 years) deaths occurred in 2008.<sup>43</sup> Analysis of the most recent global HIV prevalence data reveals a disproportionate effect of HIV in sub-Saharan Africa, with 70% of new HIV infections and HIV associated deaths in 2008 occurring within this region (Table 4.1).<sup>43</sup>

**Table 4.1:** Adults and Children Living with HIV, Newly Infected, Adult HIV Prevalence, and Deaths in Adults and Children by Region 2008<sup>43</sup>

	Adults and children living with HIV [range]	Adults and children newly infected with HIV [range]	Adult prevalence (15–49 years) (%) [range]	Adult and child deaths [range]
Sub-Saharan Africa	22.4 million [20.8–24.1 million]	1.9 million [1.6–2.2 million]	5.2 [4.9–5.4]	1.4 million [1.1–1.7 million]
Middle East and North Africa	310,000 [250,000–380,000]	35,000 [24,000–46,000]	0.2 [<0.2–0.3]	20,000 [15,000–25,000]
South and South-East Asia	3.8 million [3.4–4.3 million]	280,000 [240,000–320,000]	0.3 [0.2–0.3]	270,000 [220,000–310,000]
East Asia	850,000 [700,000–1 million]	75,000 [58,000–88,000]	<0.1 [<0.1]	59,000 [46,000–71,000]
Latin America	2.0 million [1.8–2.2 million]	170,000 [150,000–200,000]	0.6 [0.5–0.6]	77,000 [66,000–89,000]
Caribbean	240,000 [220,000–260,000]	20,000 [16,000–24,000]	1.0 [0.9–1.1]	12,000 [9,300–14,000]
Eastern Europe and Central Asia	1.5 million [1.4–1.7 million]	110,000 [100,000–130,000]	0.7 [0.6–0.8]	87,000 [72,000–110,000]
Western and Central Europe	850,000 [710,000–970,000]	30,000 [23,000–35,000]	0.3 [0.2–0.3]	13,000 [10,000–15,000]
North America	1.4 million [1.2–1.6 million]	55,000 [36,000–61,000]	0.6 [0.5–0.7]	23,000 [9100–55,000]
Oceania	59,000 [51,000–68,000]	3900 [2,900–5,100]	0.3 [<0.3–0.4]	2000 [1100–3100]
Global Total	33.4 million [31.1–35.8 million]	2.7 million [2.4–3.0 million]	0.8 [<0.8–0.8]	2.0 million [1.7–2.4 million]

## HIV in At-Risk Populations

### INJECTING DRUG USERS

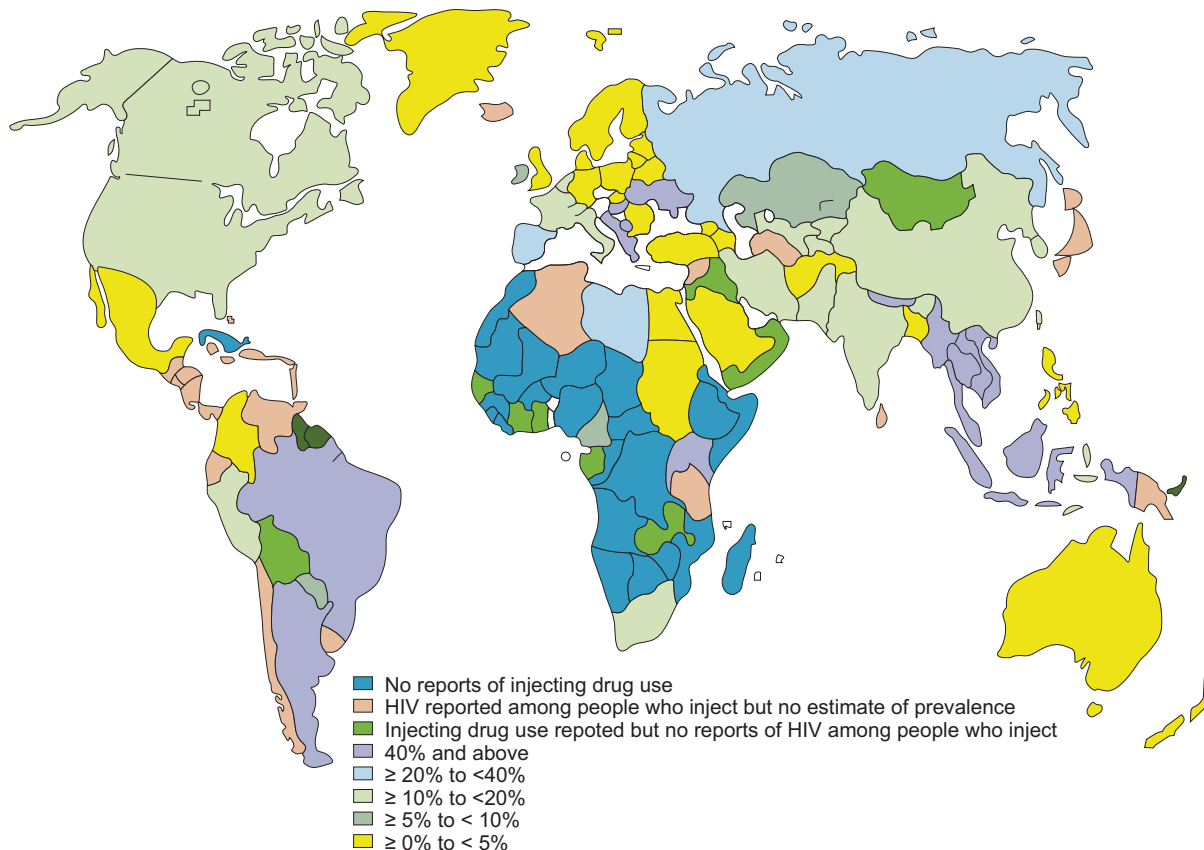
The sharing of contaminated equipment while injecting drugs is more efficient than sex at transmitting HIV, resulting in more rapid epidemics among injecting populations. Injecting is responsible for an increasing proportion of new HIV infections in many parts of the world, especially industrialized countries in Eastern Europe, South America and East and South-East Asia.<sup>45,46</sup> Countries that failed or were slow to introduce effective distribution systems for clean injecting equipment are particularly affected.<sup>47–48</sup> IDU is rare in Africa and thus has had a negligible role in the HIV epidemic in the region. IDUs epidemics are dynamic: for example, HIV was not identified among IDUs in Estonia a decade back whereas recent estimates show that the prevalence of HIV among IDU has reached around 72%.<sup>45</sup>

The findings of the Reference Group to the UN on HIV and IDU<sup>45</sup> show that:

- Globally, there are about 3.0 million (range 0.8–6.6 million) (Table 4.2) HIV positive IDUs, and HIV prevalence varies greatly between countries within the region and also within countries (Fig. 4.2).
- The national midpoint prevalence of HIV among IDUs ranged from less than 0.01% to 72% globally.
- Countries in South-East Asia, Eastern Europe and Latin America report a prevalence of above 40% in subpopulations of IDUs.
- China, Russia and USA have the highest populations of injectors and the prevalence of HIV in IDUs in all three countries is above 10%.
- There is a wide variation of HIV prevalence among IDUs within countries as well. For example, in China infection among IDUs is reported to be concentrated in 7 provinces only and in Russia the prevalence varies from 0.3% in Pskov to 74% in Biysk.

**Table 4.2:** Regional and Global Estimates HIV Positive IDUs, 2007<sup>45</sup>

Region	Estimated number of HIV positive IDUs
Eastern Europe	940,000 (18,500–2,422,000)
Western Europe	114,000 (39,000–210,500)
East and South-East Asia	661,000 (313,000–1,251,500)
South Asia	74,500 (34,500–135,500)
Central Asia	29,000 (16,500–47,000)
Caribbean	24,000 (6000–52,500)
Latin America	580,500 (181,500–1,175,500)
Canada and United States	347,000 (127,000–709,000)
Pacific Island States and Territories	500 (<250–500)
Australia and New Zealand	2500 (500–6000)
Middle East North Africa	3500 (1500–6500)
Sub-Saharan Africa	221,000 (26,000–572,000)
Extrapolated global estimates	2,997,500 (764,000–6,589,000)



**Fig. 4.2:** Prevalence of HIV among IDUs, 2007.<sup>45</sup>

## MEN WHO HAVE SEX WITH MEN

HIV prevalence rates are much higher in MSM than in general population globally (Box 4.2).<sup>49</sup> Over the past decade the incidence of HIV infection has resurged in MSM in the western world, and now there are reports of new or newly identified epidemics among MSM in Asia, Africa, and Latin America.<sup>50</sup> Testing has increased markedly in countries like USA, Canada, and the UK, which may at least partly explain the increase in diagnoses.<sup>51</sup>

Sex between consenting adult men remains criminalized in 85 countries as of 2007, including more than half of African states,<sup>49</sup> increasing the risk of HIV transmission as MSM are inaccessible to health education promotion. According to 2005 UNAIDS estimates less than 1 in 10 MSM globally have access to HIV prevention services.<sup>52</sup>

## SEX WORKERS

The prevalence of HIV in sex workers can vary considerably from country to country, within the same country, and from one type of sex worker to another. Differences in working environments, socioeconomic situation, health status, and knowledge and practice of protective measures explain some of this variation.<sup>53–54</sup> Because of their large numbers of sexual partners, sex workers in a number of countries were affected early in their country's HIV epidemics.<sup>38–40,55</sup> Since the sex industry's clientele is drawn from the population at large, often accounting for a substantial proportion of extramarital couplings,<sup>56–57</sup> the HIV prevalence among sex workers can to some extent foretell the impact of HIV in the general population. Interventions with sex workers that have proven effective at controlling HIV and other STIs include funded peer education, screening and treatment for other STIs, and the free distribution of condoms.<sup>58–61</sup> Such interventions

with sex workers have been estimated to be one of the most cost-effective HIV control strategies in developing countries.<sup>62–63</sup>

## MOTHER-TO-CHILD TRANSMISSION

Number of HIV infected children in the population depends on the prevalence of HIV in pregnant women and the availability of adequate prevention and treatment service to these women.<sup>21</sup> Majority of the 430,000 newly diagnosed children in 2008 acquired HIV through MTCT.<sup>64</sup> Multiple interventions are now available including: voluntary HIV testing of pregnant women, use of rapid testing at time of delivery and availability of antiretroviral therapy.<sup>8,21</sup> Availability of these interventions has reduced perinatal transmission all across Europe and North America.<sup>8,21,65</sup> The transmission rate has reduced in most high-income countries, from 25% to 1–2%.<sup>20</sup> However, transmission rates remains high in developing countries due to the limited availability of antiviral therapy, and difficulties with using formula milk.<sup>20</sup>

In 2005, only 9% of pregnant women were offered services to prevent HIV transmission to their newborns in middle and low-income countries.<sup>8,64</sup> MTCT remains a major problem in sub-Saharan Africa, in spite of the increased availability of antiretroviral drugs to pregnant women.<sup>43,66</sup> Similarly, a low percentage of pregnant women living with HIV have access to antiretrovirals in most parts of Asia.<sup>64</sup>

## OTHER MOBILE POPULATIONS

There are other at-risk populations that are often neglected when looking at the HIV picture. These populations include truck drivers, military personnel, and other mobile populations like refugees. HIV prevalence in military conscripts can give an indication of prevalence in the general population, as they come from all strata of general population.<sup>67</sup> Long haul truck drivers are also at high risk of HIV infection because of their large number of sexual partners, paying for sex, failure to use condoms, poor education, and lack of HIV knowledge.<sup>68–74</sup> Factors associated with increased risk of HIV for refugees include the prevalence of HIV in the host and refugee population, the prevalence of other STIs, level of sexual interaction between groups, availability of HIV prevention services, and specific risk factors like rape and sex work.<sup>75</sup>

## Regional Patterns of HIV

### SUB-SAHARAN AFRICA

Sub-Saharan Africa is the region most affected by HIV. An estimated 22.4 million people are living with HIV, including 90% of children living with HIV globally.<sup>43</sup> Approximately 2 million (1.7–2.3 million) died from HIV in the region in 2005.<sup>8</sup> Within sub-Saharan Africa, there is considerable variation between the HIV epidemics of various countries. National population-based surveys conducted between 2001 and 2008 revealed the adult national HIV prevalence is below 5% in most African countries. However, an HIV prevalence of greater than 15% was shown in 6 Southern African countries (Box 4.3).<sup>43</sup>

### Box 4.2 Prevalence of HIV in MSM in Various Regions<sup>50</sup>

- Europe: HIV prevalence in MSM ranges from 5% in Ireland to 18% in Spain in Western Europe, from 0% in Lithuania to 2.5% in Slovenia in Central Europe, and from 0% in Kazakhstan to 6% in Moscow in Eastern Europe and the former Soviet Union states.
- North America: According to the Centers for Disease Control and Prevention 48% of 1.1 million HIV positive people are MSM in the US. Similarly, in Canada half (51%) of people living with HIV are MSM.
- Oceania: MSM account for 64% of newly diagnosed and 82% of newly acquired infections in Australia. Whereas in New Zealand, 55% of HIV cases reported were MSM. In contrast only 0.1% of HIV infections are in MSM in Papua New Guinea.
- Asia: The prevalence varies widely among countries and within countries in Asia. In East Asia 33–67% of the newly reported HIV cases are MSMs. In South East Asia 0–31% MSM are infected with HIV and in South Asia 0.2–25% MSM are infected with HIV.
- Latin America: Prevalence varies from around 7% in Brazil and Nicaragua to 26% in Mexico. The average HIV prevalence among MSM across El Salvador, Guatemala, Honduras, Nicaragua, and Panama was 12%.
- Africa: The prevalence varies from around 11–38% in Kenya and 11–31% in Cape Town.



**Box 4.3** Countries with >15% HIV Prevalence in Southern Africa

- Botswana
- Lesotho
- South Africa
- Swaziland
- Zambia
- Zimbabwe

**Heterosexual Transmission**

High HIV prevalence and incidence rates in sub-Saharan Africa are mostly attributed to heterosexual transmission, leading to the region having the world's largest population of children living with HIV. Various studies, including population-based surveys, have shown a high prevalence of HIV serodiscordance among heterosexual couples in Africa, ranging from 2% in Rwanda to 13% in Lesotho and Zimbabwe.<sup>76–78</sup> A large proportion of heterosexual transmission occurs among serodiscordant couples.<sup>79</sup> One study using data from Demographic and Health Surveys (DHS) estimated that between 55% and 93% of new heterosexually acquired HIV infections among adults in urban Rwanda and Zambia occurred in the context of serodiscordant marital or cohabiting relationships.<sup>80</sup> A separate study using DHS data from 5 countries (Burkina Faso, Cameroon, Ghana, Kenya, and Tanzania) demonstrated that two thirds of HIV-infected couples were serologically discordant.<sup>81</sup> Furthermore, condom use was rare in countries such as Burkina Faso where almost 90% of cohabiting couples surveyed did not use a condom the last time they had sex.<sup>81</sup> Women and young girls are disproportionately affected by HIV in sub-Saharan Africa due to a number of factors such as physiological susceptibility and a number of social and legal disadvantages.<sup>43</sup> The ratio of women to men living with HIV is 3:2.<sup>8</sup>

**Injecting Drug Use**

Because IDU is rare in sub-Saharan Africa, it has had a negligible role in the HIV epidemic. Regardless, survey-based studies have shown that IDUs are at high risk of HIV infection in various countries, with prevalence reaching 12% in South Africa and 43% in Kenya.<sup>45</sup>

**Male Homosexuality**

Unprotected anal sex between men is an increasingly recognized risk factor for the HIV epidemic in sub-Saharan Africa.<sup>82</sup> Prevalence of HIV among MSM in sub-Saharan Africa has been listed in Table 4.3.

**Table 4.3:** Prevalence of HIV Among MSM in Sub-Saharan Africa

Kenya <sup>50,83–84</sup>	11–38%
Senegal <sup>50,85–86</sup>	21.5–22%
South Africa (Cape Town) <sup>50</sup>	11–31%
Sudan <sup>85–86</sup>	9%
Tanzania <sup>50</sup>	12%

**Mother-to-Child Transmission**

The percentage of HIV-infected women receiving antiretroviral drugs to prevent transmission to their newborn children increased from 9% in 2004 to 45% in 2008.<sup>66</sup> Although the number is decreasing, MTCT continues to account for a large number of new HIV infections in many African countries.<sup>43</sup>

**Sex Work**

Sex work is common but is now thought to contribute a smaller proportion of new HIV infections in sub-Saharan Africa where the epidemic is mature.<sup>63</sup> HIV is, however, prevalent among the sex worker population, with HIV prevalence reportedly greater than 30% in 7 African countries (Benin, Burundi, Cameroon, Ghana, Guinea Bissau, Mali, and Nigeria) and reaching 49% in Guinea Bissau.<sup>66</sup>

**ASIA**

In Asia, there were about 4.7 million people living with HIV in 2008, with an estimated 350,000 people who were newly infected and 330,000 deaths from an HIV-related illness.<sup>43</sup> The majority of the HIV infections in Asia occur in South and South-East Asia. Declines in adult HIV prevalence have been observed in Cambodia, where prevalence has fallen from 1.5% in 2001 to 0.8% in 2007. However, rapidly growing epidemics have been observed in Vietnam, Indonesia, Malaysia, and Pakistan.<sup>87</sup> In Indonesia, the number of people living with HIV more than doubled between 2001 (93,000) and 2007 (270,000).<sup>87</sup> This region has the world's most diverse spectrum of HIV transmission modes.

**Heterosexual Transmission**

Patterns of HIV transmission vary between countries in the region and also vary widely within countries. For example, in India heterosexual transmission drives the epidemic in the southern states, whereas IDU is mainly responsible in the north eastern states.<sup>88</sup> Condom promotion during commercial sex in Cambodia and Thailand have helped curb HIV spread through sexual transmission.<sup>67</sup>

**Injecting Drug Use**

IDU played a primary role in the HIV epidemics of several countries of the region.<sup>89</sup> During the late 1980s, the long-recognized centers of opium production known as the 'Golden Triangle' (in the bordering areas of Myanmar, Thailand, and the Lao PDR) and the 'Golden Crescent' (located in northwest Pakistan, the Badakhshan area of Afghanistan, and the Baluchistan area of Iran) began processing the drug into the injectable form, heroin.<sup>46</sup> The consequence in Asia was the twin epidemics of HIV and IDU during the 1990s.<sup>90–91</sup> These epidemics spread along overland heroin trafficking routes and through mobile populations, such as long distance truck drivers and migrants,



onto neighboring provinces of India and China. The injection of buprenorphine (another opiate) and methamphetamine (cheaper) subsequently increased in the region.<sup>90–91</sup> Outbreaks of HIV among IDUs occur rapidly and multifocally in their early stages<sup>38</sup> depending on factors such as frequency of sharing injecting equipment, local HIV prevalence, and the nature of drug-injecting networks.<sup>91</sup> Thus, the prevalence of HIV among IDUs ranged widely from 0% to over 90% in different settings within the region during the most recently available surveys.<sup>38–39,92</sup> While typically less than 1% of the general population is directly engaged in IDU, others can become exposed to HIV as sexual partners of injectors, both spouses and casual contacts, some of whom may be trading sex to purchase drugs.<sup>90,93</sup>

## Male Homosexuality

For majority of countries in the region, gay identity is largely considered to be a manifestation of Westernization,<sup>56,94</sup> even if tempered by local ethnic and economic forces.<sup>95</sup> In many parts of the region the practice of male-to-male sex is well documented in males for whom marriage and reproduction define a heterosexual social and sexual identity regardless of other behaviors.<sup>96</sup> In this context it can be difficult for surveillance programs to disentangle homosexual from heterosexual transmission of HIV even though male-to-male sex is common.<sup>56,96–97</sup> Male-to-male sex has not been widely addressed in behavioral surveys in the region.<sup>98</sup> In very populous countries such as China and India, there may be even more marked differences between urban and rural areas in HIV prevalence and in reporting of MSM behaviors<sup>49</sup> (Table 4.4).

**Table 4.4:** Prevalence of HIV Among MSM in Asia<sup>50</sup>

East Asia	
China	0.5–9%
Hong Kong	41%
Japan	67%
Singapore	34%
South Korea	33%
Taiwan	38.5%
South-East Asia	
Cambodia	0.7–9%
Indonesia	2–8%
Lao PDR	6%
Myanmar	29%
Thailand	17–31%
Vietnam	0–8%
South Asia	
Bangladesh	0.2%
Pakistan	3%
Nepal	3%
India	5–25%

## Mother-to-Child Transmission

HIV prevalence is increasing in antenatal clients in some parts of India.<sup>67</sup> In East, South, and South-East Asia, only 25% women of pregnant women living with HIV were receiving antiretrovirals for preventing MTCT in 2008.<sup>64</sup>

## Sex Work

The occurrence of female, male, and transgender prostitution has been extensively documented throughout Asia.<sup>39,41,56,94,99–103</sup> Migration within countries for the purposes of prostitution is ubiquitous.<sup>40,99,101,104</sup> International migration for the same purpose, a practice dating back centuries,<sup>101</sup> is also common. For example, Nepalese sex workers have long traveled to India; Shan women migrate from Myanmar to Thailand,<sup>101</sup> and Thai women to Japan.<sup>94</sup> Though prostitution is illegal in most Asian jurisdictions,<sup>40,94,99,105</sup> it is socially tolerated within many cultures and forms a significant part of local economies. In China alone there are believed to be over 3 million sex workers despite strict sanctions, with 1.5 million in India.<sup>41</sup> The “100% condom” program in Thailand, a national initiative intended to enforce condom use during all commercial sex encounters, has led to a declining HIV prevalence among sex workers in that country with clear benefits for their client base.<sup>103,106</sup> This success has encouraged neighboring countries to adopt similar programs.<sup>102</sup>

## EASTERN EUROPE AND CENTRAL ASIA

Until the mid-1990s, HIV was uncommon in this region.<sup>16</sup> Since then, HIV prevalence has increased significantly with an estimated 1.5 million people living with HIV in 2008.<sup>43</sup> The majority of those with HIV live in either the Russian Federation (69%) or Ukraine (29%) where the annual number of new HIV infection more than doubled between 2001 and 2007. The regional HIV epidemic is concentrated among IDUs. A large proportion of sex workers also inject drugs. Economic instability in parts of the region has fueled an increase in IDU, sex work, and migration, leading to the potential for the further spread of HIV in the region.<sup>16,107</sup> In the Eastern European region, changes in social attitudes to relationships and the role of family have led to liberal views on sex and substance use.<sup>107</sup>

## Heterosexual Transmission

Heterosexual transmission in the region is also rising in a steady fashion.<sup>21,88</sup> Of more concern is the growing proportion of new HIV infections that occur among women, contributing to 40% of new cases in Eastern Europe and Central Asia in 2006.<sup>108</sup> Only a minority of women was infected through use of contaminated drug injecting equipment, and most acquired HIV during unprotected sex with IDU partners.<sup>108</sup>

## Injecting Drug Use

IDU is the most important route of transmission of HIV in the region,<sup>65,88,107</sup> as injecting increased rapidly after the

collapse of Soviet Union and increasing production of opium in Afghanistan.<sup>21,107</sup> Estonia has the highest prevalence of HIV among IDUs in the world; approximately 72% of IDUs in the country are HIV positive.<sup>45</sup> There is wide variation in HIV prevalence in IDUs in Russia; from 0.3% in Pskov to 12.4% in Moscow, 32% in St. Petersburg, and 74% in Biysk.<sup>45</sup>

## Male Homosexuality

A small proportion of new HIV infections in this region are attributed to unprotected sex among men. In Eastern Europe, less than 1% of newly reported HIV cases are in MSM. In recent cross-sectional studies among MSM, the HIV prevalence ranged from 0% in Kazakhstan to 6% in Moscow in Eastern Europe and Central Asia.<sup>50</sup>

## Mother-to-Child Transmission

Effective antiretroviral treatment is now available to prevent mother-to-child HIV transmission in the region. Pregnant women are tested on a large scale in the Russian Federation and those with a positive confirmatory test must choose between abortion and prophylactic treatment.<sup>21</sup>

## Sex Work

There is an increasing frequency of STIs and IDU in the flourishing sex industry of the region, threatening to contribute to the spread of HIV.<sup>21</sup> Prevalence studies among sex workers have found significant levels of HIV infection in Russia, 15% among 123 prostitutes attending outreach programs in 2000 in Moscow and 17% among 192 injected-drug using prostitutes in 1999 in St. Petersburg.<sup>21</sup> However, the prevalence seems to be relatively low (around 2%) in rest of the region.<sup>109</sup>

## WESTERN AND CENTRAL EUROPE

The epidemic started in late 70s and early 80s in both Western and Central Europe.<sup>16</sup> In Western Europe 25,241 new cases were diagnosed in 2006 whereas 1,805 cases were diagnosed in Central Europe.<sup>110</sup>

## Heterosexual Transmission

Heterosexual transmission is the most common route of HIV transmission in both Western and Central Europe accounting for 54% and 52% of all new infections in 2006, respectively.<sup>110</sup> However, heterosexual transmission remains concentrated in specific subgroups of the population rather than the general population.<sup>109</sup>

## Injecting Drug Use

Injecting increased in the region in the 1990s as Eastern Europe and Central Asia acted as the drug trafficking routes for heroin from Afghanistan.<sup>21</sup> IDU accounted for 8% and 16% of new infections in Western and Central Europe in 2006, respectively.<sup>110</sup>

and injecting may be increasing in some countries including Italy, the Netherlands, and Spain.<sup>109</sup>

## Male Homosexuality

Throughout Europe there are wide differences in the prevalence of HIV among MSM in community settings, with a higher prevalence reported in those countries with larger and more visible MSM populations than in countries with smaller MSM populations.<sup>111</sup> HIV prevalence among MSM ranged from 5% in Ireland to 18% in Spain in Western Europe and from 0% in Lithuania to 2.5% in Slovenia in Central Europe.<sup>50</sup> According to Euro HIV, the number of new HIV cases in MSM almost doubled, from 2538 to 5016 during 1999–2006 in 13 Western European countries and similarly, in Central Europe, the number of new cases doubled although the actual number was small, 130 in 1999 to 295 in 2006. Homosexual transmission was responsible for more than 50% of all new reported cases in many Central European countries, such as Hungary, the Czech Republic, Slovakia, and Slovenia.<sup>50</sup>

## Mother-to-Child Transmission

Availability of perinatal HIV prevention programs has decreased the MTCT all across Europe.<sup>21,65</sup>

## Sex Work

In Central Europe, sex work has grown due to economic conditions and widespread criminality, and many sex workers are also IDUs.<sup>107</sup> Although the data on HIV prevalence among sex workers in Western Europe is very sparse, available data shows that prevalence is low (around 2%) among noninjecting female sex workers.<sup>109</sup> Male sex workers, transvestites, and migrant sex workers are more at risk of HIV.<sup>109</sup>

## LATIN AMERICA AND THE CARIBBEAN

The epidemic started in late 70s and early 80s in the region.<sup>16</sup> Sexual transmission and use of contaminated injecting equipment among the poor and unemployed remain the dominant modes of transmission.<sup>8</sup> The Caribbean has been profoundly affected by HIV with adult HIV prevalence higher than every other region outside sub-Saharan Africa.<sup>43,67,112</sup> A decline in the incidence of HIV has occurred in some Caribbean countries in the past decade and HIV prevalence has stabilized.

## Heterosexual Transmission

In Latin America the epidemic was initially in MSM and IDUs. However, there has been a substantial increase in heterosexual transmission in all countries of the region. In the Caribbean the main mode of transmission is heterosexual sex, often linked to sex work. In Latin America, women comprise 20–30% of HIV positive adults,<sup>65,88</sup> and in the Caribbean they comprise around 53%.<sup>88</sup>

## Injecting Drug Use

Although rare in most of the Caribbean, IDU is an important route of transmission in some countries of the region including Argentina, Brazil, Chile, Paraguay, and Uruguay and some parts of Mexico, Bermuda, and Puerto Rico.<sup>67,88</sup>

## Male Homosexuality

Recent studies in the Caribbean and Latin America have shown that HIV transmission is increasingly occurring among MSM in urban centers, with prevalence varying between 5% and 20%.<sup>113</sup> See Table 4.5 for prevalence in various countries. The HIV incidence in MSM in Central American countries was 5 per 100 person-years in 2007.<sup>50</sup>

## Mother-to-Child Transmission

Heterosexual transmission prevails in the Caribbean with an HIV prevalence of up to 8% in pregnant women in Haiti.<sup>65,88</sup> In Brazil, MTCT accounts for 90% of cases for children under 13 years; similarly, in Argentina 96% of cases among children are due to MTCT.<sup>112</sup>

## Sex Work

There has long been sex tourism in the Caribbean leading to the link between sex work and HIV. Migrant sex workers also represent a vulnerable population for HIV.<sup>114</sup> Multiple risk factors for HIV have been identified in the region among sex workers who also use drugs, including unprotected sexual activity with multiple partners, violent victimization and migration between high and low HIV prevalence areas.<sup>114</sup>

## NORTH AMERICA

The HIV epidemic started in late 70s and early 80s in North America.<sup>16</sup> In the US, most people with HIV have high level access to medical care.<sup>65</sup> Unsafe sexual practices among MSM and the use of contaminated injecting equipment remain the

major modes of transmission; however, an increase in heterosexual transmission has been seen in women and members of minority ethnic groups.<sup>8,65</sup>

## Heterosexual Transmission

Although almost three quarters (74%) of HIV positive people in the US are males, the proportion of women is increasing.<sup>8</sup> There is a large discrepancy between the prevalence rates among non-Hispanic Blacks and other racial/ethnic minority groups and the general population.<sup>115</sup>

## Injecting Drug Use

There has been a decrease in the proportion of HIV infections acquired through IDU. However, like other modes of transmission, HIV through injecting affects the racial and ethnic minorities disproportionately in the US.<sup>116</sup>

## Male Homosexuality

In both Canada and the US, almost half of the people living with HIV are MSM: 48.1% of 1.1 million HIV positive people living in the US in 2006<sup>117</sup> and 51% of 58,000 people living with HIV in Canada.<sup>50</sup> Out of the 56,300 new infections in the US in 2006, 53% were in MSM and out of the new infections in men, 72% were in MSM. Of new infections in MSM, 46% were in whites, 35% were in blacks, and 19% were in Hispanics.<sup>50</sup> Despite advances in HIV care, almost 6,000 MSM with HIV in the United States died in 2005.<sup>118</sup>

## Mother-to-Child Transmission

Multiple interventions like voluntary HIV testing of pregnant women, use of rapid testing at time of delivery and availability of antiretroviral therapy has decreased the MTCT tremendously, from approximately 1,700 per annum in the 1990s to 145 in 2002.<sup>8</sup>

## Sex Work

Sex work remains illegal in the United States except for a couple of counties in Nevada and the government of the United States takes a strong stance against sex work including declining all grants overseas aid to any HIV/AIDS projects that do not 'explicitly oppose' sex work.<sup>119</sup> Thus, little data is available for HIV in sex workers and their clients. Like Western Europe, HIV cases among sex workers in the US are attributed to injecting rather than sexual transmission.<sup>119</sup>

## MIDDLE EAST AND NORTH AFRICA

There is only limited data on the prevalence of HIV in the region. The epidemic started in the late 80s,<sup>16</sup> and the available data shows that HIV prevalence in Middle East and North Africa (MENA) is low, with national prevalences around 0.2%, except Sudan where the prevalence is estimated to be 2%.<sup>8,88</sup>

**Table 4.5:** Prevalence of HIV Among MSM in Latin America and Caribbean<sup>50</sup>

Bolivia	21%
Brazil	7–10%
Colombia	19%
Ecuador	15%
El Salvador	15%
Jamaica	32%
Mexico	26%
Nicaragua	8%
Paraguay	13%
Peru	10–22%
Trinidad and Tobago	20%

## Heterosexual Transmission

The main mode of transmission in the region is heterosexual contact.<sup>8,88</sup> Although sexual behavior data remains limited; multiple partnerships, premarital and extramarital relationships, casual sex, and contact with female sex workers are reported in most countries with significant variations that affect sexual transmission.<sup>120</sup>

## Injecting Drug Use

There has been increasing IDUs in the region because of the changing drug-trafficking routes.<sup>121</sup> Injecting as the mode of transmission is increasing in some countries especially Iran and Libya,<sup>88,120</sup> and also Bahrain, Algeria, Egypt, Kuwait, Morocco, Oman, and Tunisia.<sup>121</sup> Overall, HIV prevalence among IDUs is in the low to intermediate range, 0.2% of population in the region, compared to global figures.<sup>120</sup>

## Male Homosexuality

Little is known about the prevalence of HIV among MSM in MENA, as it is strictly prohibited in most countries on religious grounds. In Sudan, the prevalence ranged between 8% in insertive MSM and 9% in receptive MSM, and it was 6% in MSM in Egypt.<sup>50</sup>

## Mother-to-Child Transmission

In the MENA region below 1% of pregnant women are HIV positive.<sup>120</sup> Less than 200 pregnant women infected with HIV received antiretroviral treatment out of an estimated number of 13,400 HIV-infected pregnant women in 2008.<sup>64</sup>

## Sex Work

Sex work is a hidden trade in most MENA countries due to religious and government laws. Thus, data on HIV prevalence in sex workers is very difficult to obtain. Prevalences of 0.1% to 1% among adult female sex workers have been reported.<sup>120</sup> In Djibouti sex work is less hidden compared to the rest of the region.<sup>121</sup>

## OCEANIA

The epidemic started in late 70s and early 80s<sup>16</sup> and the overall HIV prevalence in Australia, New Zealand, and Fiji remains low at or below 0.1%. However, the epidemic in Papua New Guinea is growing rapidly with the number of people infected with HIV increasing about 30% per year since 1997.<sup>8</sup>

## Heterosexual Transmission

In Australia, only 20% of HIV infections were due to heterosexual transmission between 2000 and 2006, up from 15% between 1993 and 1999.<sup>122</sup> Casual and commercial sex, mostly heterosexual is driving the epidemic in Papua New Guinea and rape, sexual

aggression, and other forms of violence against women is aiding the epidemic.<sup>67</sup>

## Injecting Drug Use

Levels of HIV are very low (<1%) in IDUs in Australia and New Zealand despite a relatively higher prevalence of injecting; this is because of the geographic isolation and the early introduction of needle and syringe, targeted education, and opiate substitution programs.<sup>45</sup>

## Male Homosexuality

In Australia and New Zealand, HIV continues to be an infection that disproportionately affects MSM<sup>51,67,122</sup> and a 2008 study shows that HIV prevalence in homosexual men in large Australian cities is now less than 10%.<sup>51</sup> In 2005, 76% of new HIV diagnoses and 88% of newly acquired HIV infections were in MSM.<sup>51</sup> HIV prevalence among MSM is estimated to be 1% in 2007 in New Zealand, and 5.5% of the 2,872 reported HIV cases during 1985-2007 were in MSM.<sup>50</sup> In Papua New Guinea 0.1% of the total of reported HIV infections were in MSM.<sup>50</sup>

## Mother-to-Child Transmission

In Papua New Guinea, 1% of pregnant women tested HIV positive at antenatal clinics in Port Moresby and 2.5% of pregnant women were HIV positive in Lac in the Central Highlands.<sup>67</sup>

## Sex Work

The overall prevalence of HIV among the sex workers was more than 10 times than that of the general population in Papua New Guinea.<sup>123</sup> HIV is rare (<1%) among female sex workers in Australia and New Zealand because of high condom use at work and the low prevalence of HIV in IDUs.

## Conclusion

HIV morbidity and mortality continues to increase in many parts of the world despite major advances in the understanding of HIV in the past two decades and increasing access to antiretroviral treatment.<sup>8</sup> HIV has become one of the leading causes of premature death in men and women aged 15–59 years.<sup>8</sup> The following interventions have been suggested for limiting the impact of HIV in developing countries<sup>65</sup>:

- Strengthened HIV surveillance
- Life skills (including HIV) education for youth
- Widespread voluntary testing and counseling
- Health education, condom promotion, and strengthened STD control, including special programs for sex workers
- Blood safety
- Prevention of perinatal transmission
- Treatment services for drug users (including provision of sterile injection equipment)
- Appropriate HIV care



- Strengthened tuberculosis control
- Strengthened education of girls, promotion of women's rights and status
- Services for orphans

### Summary

HIV infection spreads through three major routes: sexual, blood borne, and mother-to-child. Most infections are caused by the type 1 virus, which is divided into three groups based on the genome difference: M, N, and O. There were an estimated 33.4 million people living with HIV in 2008; with an estimated 2.7 million new HIV infections (2.3 million adults and 0.4 million children below 15 years) and 2 million (1.7 million adults and 0.3 million children below 15 years) deaths in the year. Sub-Saharan Africa is disproportionately affected by HIV and 70% of the deaths associated with the infection in 2008 were in the region with many countries having an HIV prevalence of more than 15%. Different modes of transmission and different at-risk populations drive the epidemic in various parts of the world. Injecting is responsible for an increasing proportion of new HIV infections in industrialized countries in Eastern Europe, South America, and East and South-East Asia. HIV has resurged in MSMs in the western world over the past decade with increasing reports of new or newly identified epidemics among MSM in Asia, Africa, and Latin America. The prevalence of HIV in sex workers varies considerably from country to country, within the same country and from one type of sex worker to another; this is explained by the differences in working environments, socioeconomic situation, health status, and knowledge and practice of protective measures. Briefly, HIV morbidity and mortality continues to increase in many parts of the world despite major advances in the understanding of HIV in the past two decades and increasing access to antiretroviral treatment.

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# 5

## Sexual Behavior and Sexually Transmitted Infections

Kaye Wellings

### Introduction

An understanding of trends and patterns in sexual behavior is essential to the prediction and prevention of STI transmission. Reliable data are needed to understand the epidemiology of sexually transmitted infections, to design effective interventions aimed at reducing transmission, and to assess progress towards these goals. Data from comparative studies are vital in guiding the effective targeting and tailoring of interventions to specific social groups and contexts. Importantly, too, empirical evidence is needed to correct myths in public perception of behaviors. In this chapter, we describe current trends and patterns in sexual behavior and their implications for the prevention of STI transmission.

### Trends and Patterns of Sexual Behavior

The past half century has seen marked changes in sexual behavior. These have occurred in response to demographic changes: in the age structures of populations, in the timing of marriage, and in the size of families. The scale of mobility and migration between and within countries has increased. The increase in intra and international travel, particularly, has played its part in increasing possibilities for the transmission of STIs, but so too have changing patterns of labor, rural to urban movement, and social disruption due to war and political instabilities.

Attitudes towards sexual behavior have changed significantly in recent times. Global communications, including the internet, have had a bearing on social norms, transporting Western sexual images to more conservative societies, particularly those in which advances in information technology have been rapid. The increasing accessibility of pornography has provided new imagery surrounding sexual practices and relationships.<sup>1</sup> Public health policy and practice has also impacted on sexual behavior. Advances in contraception have increasingly freed sexual expression from its reproductive consequences; access to sexual health services has increased and few areas have been unaffected by efforts to prevent HIV transmission. The HIV epidemic has significantly influenced the context in which sexual behavior occurs, providing the impetus to public discussion of sexual matters, to research

on the subject, and to innovation in interventions designed to improve sexual health.

### RISK BEHAVIORS

Given the rapid pace of social change, sexual behavior has perhaps changed less over time than might have been supposed. The widespread assumption that onset of sexual activity is occurring at ever younger ages, for example, is not borne out by the evidence. Considerable public health interest surrounds age at onset of sexual activity, since early sexual intercourse is more likely to be nonconsensual, to be regretted, to be unprotected against unplanned pregnancy and infection, and to be associated with larger lifetime numbers of sexual partners.<sup>2-4</sup> The evidence of an association between age at sexual debut and risk of sexually transmitted infections after adjusting for numbers of life time sexual partners, is equivocal, but has been demonstrated in some studies.<sup>5</sup>

Cross-nation comparisons show marked regional and gender variations in the age at which sexual activity begins but no universal trend toward earlier sex, at least for women.<sup>6</sup> In countries in which first intercourse still occurs predominantly within marriage, the tendency towards later marriage has been accompanied by a trend towards later sex among young women. For women, median age at first intercourse is lower in regions in which early marriage is the norm, for example, in South Asia, Central, West and East Africa, and higher in Latin America and in some countries of the Middle East and South-East Asia. For men, age at first intercourse is, in general, not linked to age at marriage. In most African and Asian countries men start sex later than women. Gender differences are less pronounced in the richer countries of the West. In industrialized countries, sexual activity before age 15 has become more common in recent decades but the prevalence is low.

The shift toward later marriage has led to an increase in premarital sex,<sup>7</sup> the prevalence of which is higher in high-income than low- and middle-income countries, and among men compared with women<sup>8</sup> (Fig. 5.1a,b). Marriage is often held to be a protective factor in relation to STI transmission, yet marriage

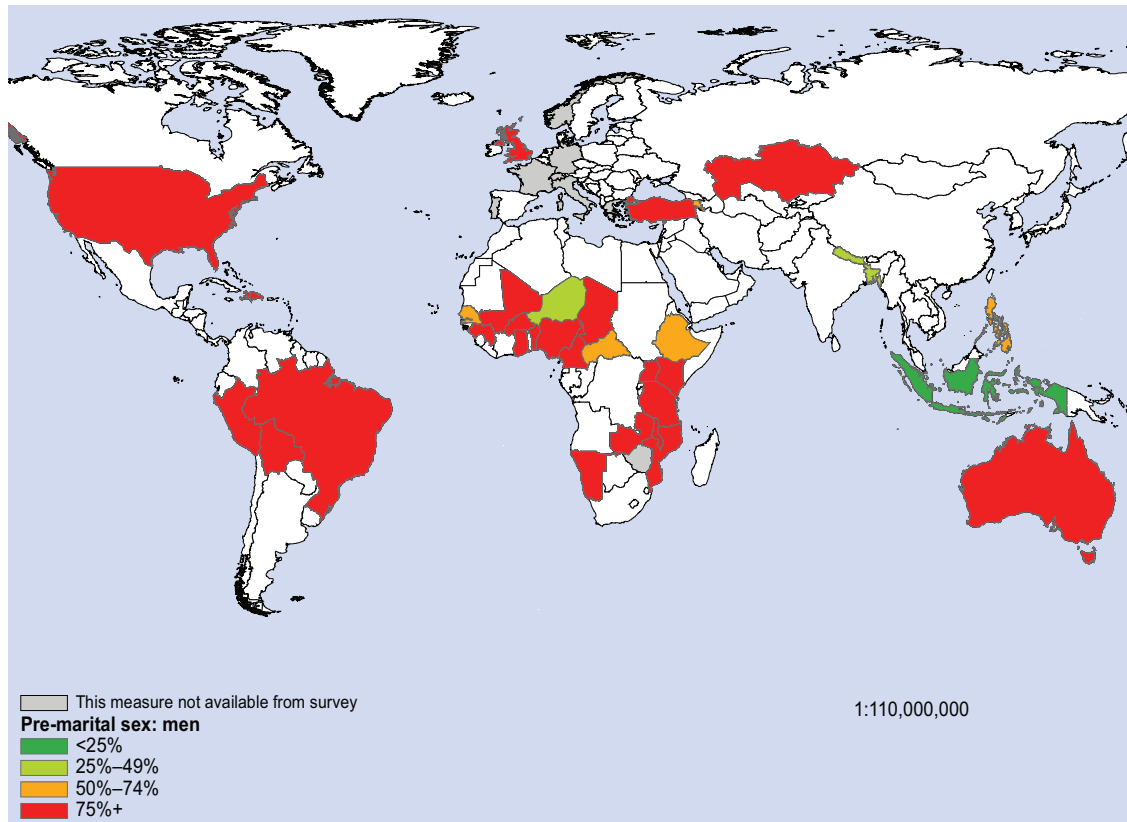


Fig. 5.1a: Prevalence of premarital sex among men.

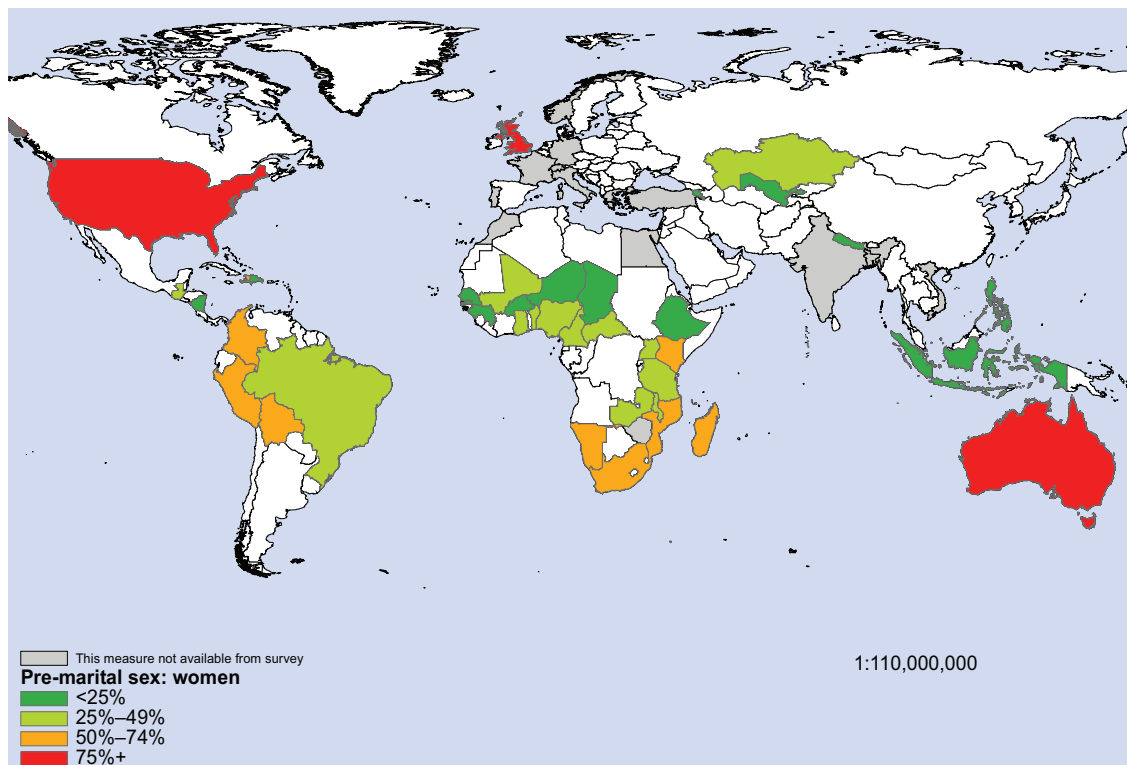


Fig. 5.1b: Prevalence of premarital sex among women.

does not necessarily ensure safer early sexual experience. In Kenya and Zambia, for example, research has shown that the sexual health benefits of marriage for women were offset by higher coital frequencies, lower rates of condom use and their husband's risk behavior.<sup>9</sup> Married women may find it more difficult than single women to negotiate safer sex and fewer use condoms for family planning. In Asian countries where early marriage is encouraged to protect young women's honor, early sexual experiences can be coercive and traumatic.<sup>10,11</sup>

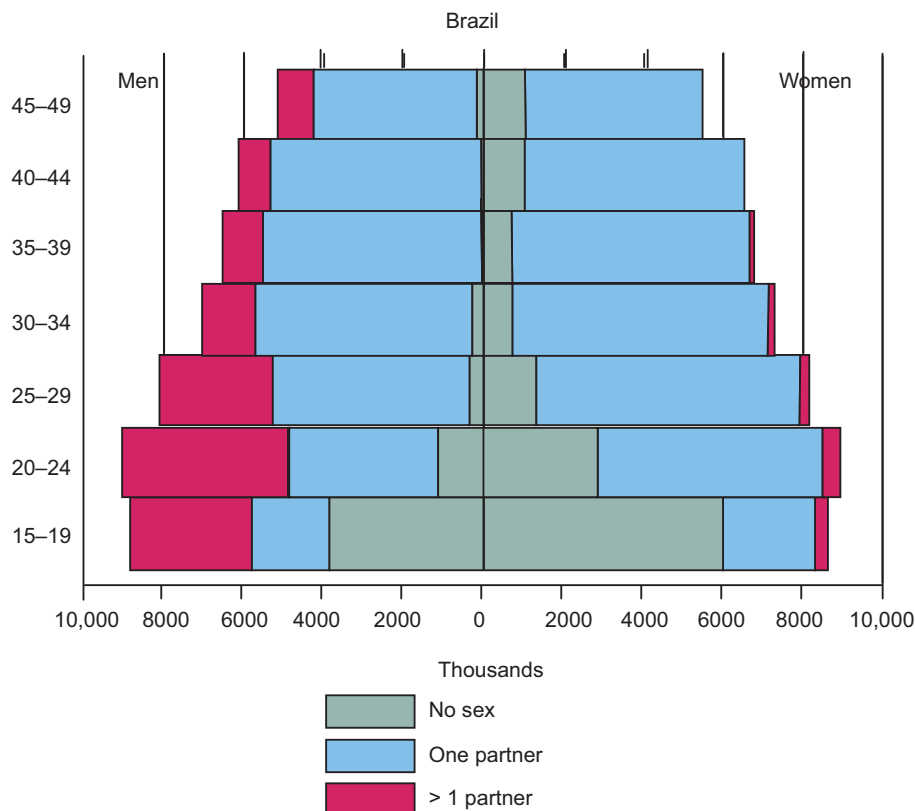
Despite the prevalent view that sexual activity is highest in young single people, the evidence is that married people have the most sex. Sexual activity among those who are single tends to be sporadic and, in most regions, well under half of unmarried non-virgins report having had sex in the last month. Single men and women in many countries in Africa are relatively inactive sexually, in marked contrast to those in industrialized countries where two-thirds and three-quarters, respectively, report recent sexual activity.<sup>6</sup>

Multiple partnerships are a key risk behavior for STIs. The majority of people report only one sexual partner in the past year; only a minority of men and women report multiple partnerships in that time period. The prevalence of multiple partnerships varies regionally but is notably higher in industrialized countries.<sup>6</sup> Having two or more sexual partners in the past year is more common among men than women, and reported levels are higher in industrialized countries. Only in some industrialized countries are men and women more equal in the proportions

reporting multiple partnerships. Some of the gender difference is attributable to reporting bias. In countries like Africa, for example, in which young people greatly outnumber older people, the difference can be largely explained by the age structure and patterns of age mixing, that is, older men having sex with younger women (Fig. 5.2a,b,c). Median age differences between spouses in Africa are comparatively long. Age mixing may be an important determinate of STI/HIV prevalence in adolescents and indeed one of the few risk behaviors shown to be associated with increased prevalence in heterosexual<sup>12</sup> and homosexual<sup>13</sup> encounters is having an older male partner.

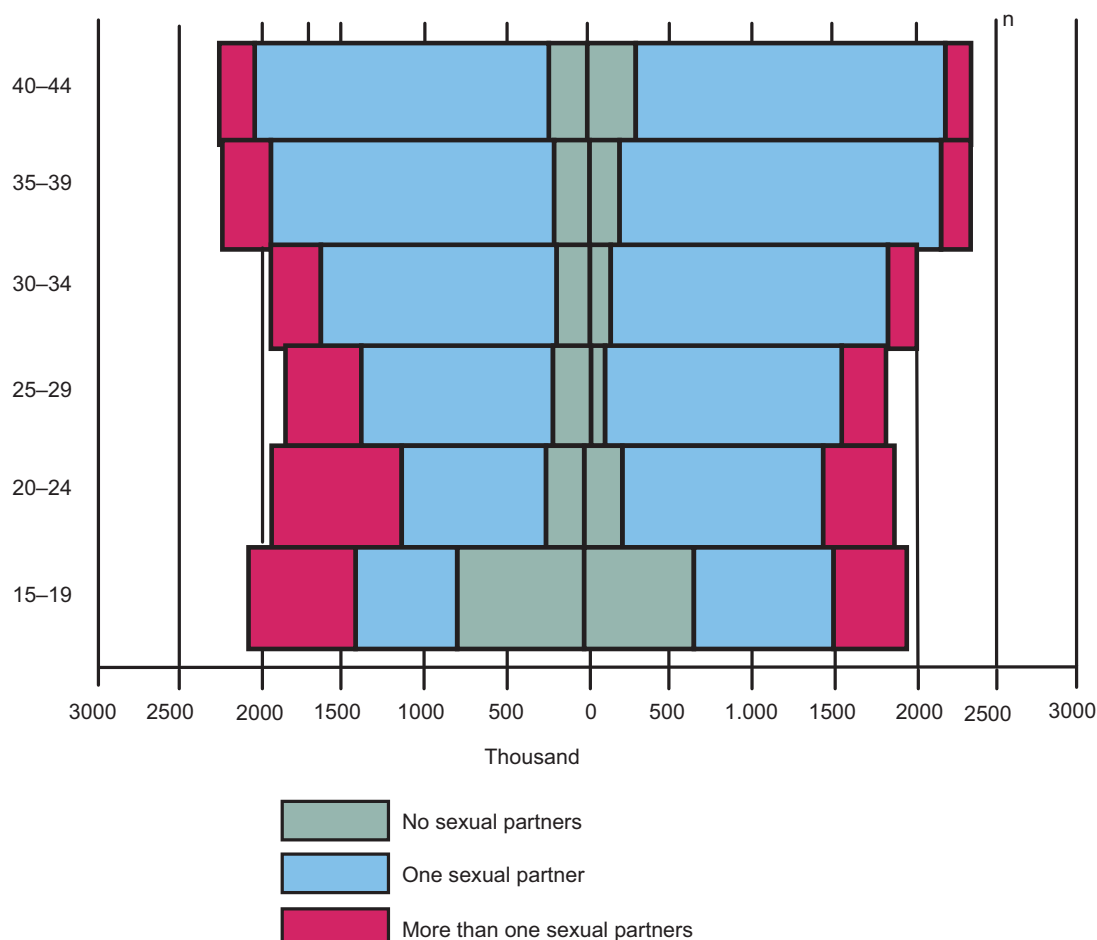
In some countries of South America such as Brazil, however, more men than women report having one or more recent sexual partners in all age cohorts. There the median age difference between partners is shorter and patterns of age mixing and age structure do not account for the gender differences in sexual partnerships. The Latin "macho" culture may encourage men to over report, and women to under report, sexual activity.

In this context, we need to distinguish between lifetime sexual partnerships conducted serially and concurrent partnerships. Concurrent sexual partnerships play a fundamental role in accelerating the spread of STIs and HIV.<sup>14–18</sup> Defined as those in which one or both of the partnership members have other sexual partners while continuing sexual activity with the original partner, concurrent partnerships have been shown to permit more rapid spread of STIs than the same rate of new sequential partnerships.<sup>16</sup>

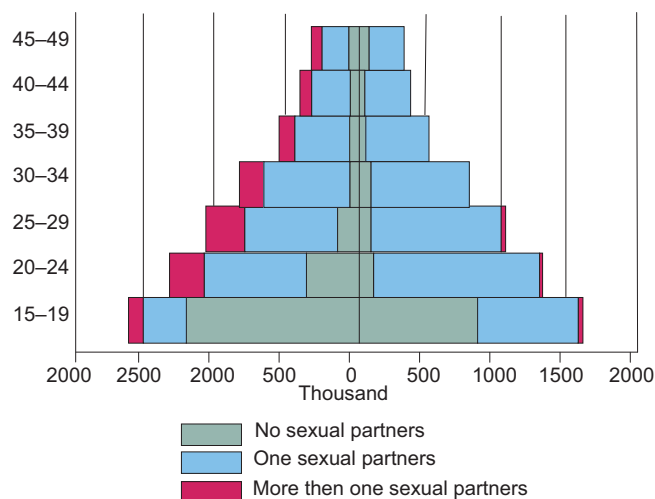


**Fig. 5.2a:** Population distribution by age and sex and number of sexual partners in the past year, 15–49 year olds (Brazil).





**Fig. 5.2b:** Population distribution by age and sex and number of sexual partners in the past year, 15–49 year olds (Britain).



**Fig. 5.2c:** Population distribution by age and sex and number of sexual partners in the past year, 15–49 year olds (Uganda).

Concurrent sexual partnerships have been most strongly associated with the transmission of bacterial sexually transmitted infections. Viral sexually transmitted infections such as

human papillomavirus (HPV),<sup>18</sup> and *Chlamydia trachomatis* have, however, also been shown to be associated with partner concurrency.<sup>19</sup> Concurrency facilitates transmission by shortening the time between sexual contacts among infected and susceptible persons, particularly during the highly infectious period.<sup>20</sup> But other factors associated with concurrency, such as type of relationship,<sup>20,21</sup> disassortative mixing,<sup>20,21</sup> higher levels of unprotected sex,<sup>16,18</sup> and the use of alcohol and other drugs<sup>18</sup> also play a part. Unfortunately, the comparative empirical data seldom capture whether partnerships are conducted concurrently or serially. However, there is evidence to show that although lifetime numbers of sexual partners may be lower in some African countries, concurrent relationships may be more common and of longer duration than in other regions.<sup>22–25</sup>

Intimate partner violence has also been shown to increase the risk of sexually transmitted infections, through decreased autonomy and inability to ensure condom use, principally on the part of women.<sup>26</sup> Understanding the link between violence and inability to use condoms contributes to an understanding why some sex worker populations are particularly vulnerable to elevated rates of STI infection compared with the general population.<sup>27,28</sup>

Estimates of lifetime prevalence of sexual violence by an intimate partner from the WHO study on gender-based violence range between 10% and 50%.<sup>29</sup> There is an association between early sexual experience and sexual violence; in more than half the WHO settings, over 30% of women who reported first sex before the age of 15 years described having been forced to do so and three quarters of women who had been abused since the age of 15 identified the perpetrator as their intimate partner.

The apparent lack of association between regional variation in sexual behavior and regional variation in sexual health status, and in particular, the comparatively high prevalence of multiple partnerships in the West compared with parts of the world with far higher rates of STIs and HIV, for example African countries, may appear counterintuitive. It is likely to be explained partly by higher rates of concurrency in some countries, but also by lower rates of condom use. The predominant form of risk reduction practice in relation to STIs, condom use, has increased in prevalence almost everywhere—in some cases, for example, Uganda, dramatically so. In industrialized countries too, the rise in condom use has been impressive. Yet rates of use are still low in many developing countries and this is likely to be attributable to factors relating to access and service provision. Even in the richer countries prevalence of use is not sufficiently high to offset the risk posed by increases in the prevalence of other risk behaviors.<sup>30</sup> There are few comparative data on the consistency with which condoms are used. Men and women who report concurrent sexual partners are more likely to report more recent episodes of unprotected sex<sup>18</sup> and their increased risk of STI transmission may be compounded by the low prevalence of condom use.<sup>16</sup>

## RISK GROUPS

In general, a focus on behaviors rather than groups is more useful in a public health context, since risk behaviors are not necessarily limited to the groups thought of as high-risk, and the changing behavior of men and women with situation defies efforts to position them discretely into groups. Many men who have sex with men (MSM), for example, also have sex with women and those who do are less likely to practice safer sex.<sup>31</sup> An individual's risk depends also on their partner's risk. Monogamous women in many parts of the world are rendered more susceptible to sexually transmitted infection on account of their partner's risk behavior, yet may be unable to negotiate condom use.<sup>32</sup>

Nevertheless, although STIs can be contracted by all sections of society, some identifiable groups are more vulnerable than others. Young people, MSM and men and women affected by poverty and social exclusion are disproportionately affected. A major problem for intervention research is that, as a general rule, the higher the risk in terms of STI acquisition, the greater the challenges in terms of effective sampling and data collection.

MSM, a particularly high-risk group for HIV and other STIs, are a case in point. The socially censored nature of same sex activity may lead to under reporting and may also account for its absence from the research agenda. A recent review of the prevalence of same sex activity among men, for example, identified 67 studies,<sup>33</sup> yet none were from Africa, the Middle East, or the English speaking Caribbean.

Clients of sex workers are important bridging groups in the transmission of STIs and HIV to wider sexual networks. Transactional sex<sup>1</sup> may be a factor explaining the fact that men are more likely to report concurrency than women.<sup>18</sup> In countries with wide gender differences between men and women in the prevalence of premarital sex, young men are more likely to report sex with sex workers.

Mean numbers of sexual partners are not surprisingly higher among male and female sex workers. Moreover, female sex workers are often exposed to violence, and those who are have diminished capacity for harm reduction and have greater prevalence of STI symptoms.<sup>34</sup> However, the primary risk for STIs among sex workers is unprotected sex with high-risk regular partners.

The use of different definitions of sex work makes it difficult to make comparisons of the prevalence of transactional sex across time and place. The continuum of sexual exchange ranges from expectation of gifts or favors within personal relationships, to more formal trading of sex for money. Estimates of the proportion of men who are clients of sex workers range from 1%–14% in different regions.<sup>33</sup> The proportion of men reporting having obtained “sex in exchange for money, gifts, or favors” in the past year is highest in countries of Central and Southern Africa (medians: 13.6% and 11.3%, respectively), followed by Eastern and West Africa (9.8% and 8.9%, respectively). More recent African surveys using a more restricted definition of “paying for sex” have reported lower prevalences. Estimates in other areas, Latin America, Eastern Europe, Central Asia, and West European countries were below 3%.<sup>33</sup>

## IMPORTANCE OF SOCIAL CONTEXT

The variation in patterns of sexual behavior, between regions and between sub-groups of the population, reflects the powerful role of environmental factors in shaping behavior and its consequences for sexual health. The striking gender differences in sexual behavior, for example, are largely determined by social norms in specific cultural contexts. Differences between men and women in terms of sexual behavior are most pronounced in the less industrialized countries.<sup>6</sup> Men report more premarital sex and multiple partnerships than women in all but the more industrialized countries. The sexual double standard, whereby restraint is expected of women, while excesses are tolerated for men, compounds sexual health problems for both men and women. Women may be disadvantaged in protecting their sexual

\*In addition to the formal trading of sex for money, sex may be exchanged for gifts or favors within personal relationships, and hence the term “transactional sex” is sometimes preferred.

health where their partner is senior to them in age and/or superior in status; and where they are beholden to a man for favors, goods, or money in return for sex.

Poverty, deprivation, and unemployment also contribute to personal risk. Lack of local employment opportunities may drive men and women to sell sex or travel greater distances to work.<sup>35</sup> Being away from home is associated in both developed and developing countries with concurrent partnerships, disruption of existing partnerships and an increase in risk behaviors.<sup>36–38</sup>

Possibly, the most powerful influences on human sexuality are the social norms governing its expression. Morals, taboos, laws, and religious beliefs employed by societies the world over circumscribe and radically determine the sexual behavior of their citizens. Such strictures may have been instituted to protect well-being and rights, yet they may also hinder attempts by both men and women to protect their sexual health, and they also strongly influence the selection of acceptable public health messages. In some countries, Brazil for example, condoms are available to young people in schools; in others, parts of Indonesia for example, possession is a criminal offence.

Nowhere are the social norms more strongly felt than in the area of homosexual activity. In some parts of the world, sex between men can be celebrated in public parades of pride, in others it carries the death penalty. Whether sexual orientation is innate is an issue that is hotly contested in scientific circles, but more important from a public health perspective is the issue of sexual identity, a term used to refer to the way in which an individual sees himself and is seen by others. Where cultures stigmatize homosexual behavior and relationships, men and women may be wary of assuming an openly gay identity. Behaviors that are discriminated against may be driven underground, thwarting public health initiatives to protect sexual health.

## Implications for Interventions to Improve Sexual Health

Sexual behaviors present particular challenges to public health. The practices involved are for the most part personal and private, and they are often stigmatized and discriminated against. This has consequences for prevention of STIs at a number of levels. Men and women may feel unable to talk about safer sex; they may feel disinclined to seek help; politicians may be unwilling to support provision of services for some populations; and service providers may feel unable to reach those in greatest need of help, or have negative attitudes towards them.

Where behaviors are criminalized, they present even greater challenges for intervention. In general, laws protect the young and those vulnerable to coercion and exploitation, but they may also impede safer sex practices.<sup>39</sup> Illegal practices are more likely to be engaged in a furtive or clandestine manner, and opportunities for protection are constrained. In most parts of the world, for example, aspects of sex work are criminalized. As a result, sex workers have little legal protection and may easily be exploited or abused by clients, coworkers, and law enforcement officials.<sup>28</sup> The isolation and disempowerment of sex workers, enforced

by the threat of violence, may create barriers to negotiating safe sex practices, thereby increasing the risk for STIs. The success of preventive strategies may therefore depend, not only on acceptance of sexual practices which are socially censured, but it may also depend on more radical action, on engaging with policy and law makers to effect shifts in social norms and, in some instances, in influencing legislative reform. Condom use is uncommon among sex workers in India<sup>40</sup> for example, where commercial sex is heavily socially proscribed, but is near-universal in Mexico,<sup>41</sup> where public health agencies have actively and openly engaged in cooperation with female sex workers.

Interventions encouraging adoption of risk reduction practices remain a cornerstone of sexual health promotion but the evidence is that they need to be targeted and tailored to individual needs and circumstances to be effective. Multiple messages are needed, which respect diversity and preserve choice. A focus on enabling young people to have sex only when they are ready to do so has obvious value, given the evidence that first intercourse is retrospectively regretted by many women, and some men. Yet, abstinence may not be an appropriate message for those for whom first sexual experience is not consensual, where the sexual abuse of young people is common, and where the need for survival may force young people to sell sex. Effective intervention design will also focus on behaviors, rather than identity.

The strong contextual influences on sexual behavior have clear implications for intervention. Given the diversity of sexual behavior, a range of preventive strategies are needed to protect sexual health. Approaches are needed that focus not only on motivating individual behavior change, but also on the social context in which sex occurs. Although influencing individual risk behaviors is crucial to improving sexual health, efforts are needed to address the broader determinants of sexual behavior, particularly those relating to the social context. Comprehensive behavioral interventions are needed that take account of the social context in mounting individual level programs; attempt to modify social norms to facilitate uptake and support maintenance of behavior change; and tackle the structural factors contributing to risky sexual behavior. The diversity of sexual behavior needs to be respected in a range of approaches tailored to whole societies, and to particular groups and individuals within them.

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# Surveillance for Sexually Transmitted Infections and HIV

Rebecca Guy

## 6

### Introduction

The primary role of public health surveillance is to guide the planning and evaluation of policy and programs, through the collection, analysis, and interpretation of various forms of statistical information.<sup>1</sup> This chapter focuses primarily on HIV, syphilis, gonorrhea, and chlamydial infection, and the syndromes they cause, as these pathogens are the main focus of HIV/STI control programs. It is generally considered to be a role of governments to plan and fund surveillance systems, but it is also understood that they do so through various forms of partnership with community agencies who collect, interpret, and make use of surveillance data. Surveys for HIV prevalence or HIV-related risk behavior may be undertaken by public health agencies, or by research teams working in parallel to, or on behalf of government.

### Important Attributes of Surveillance

Guidelines and recommendations for HIV surveillance have been developed by several organizations over the past 2 decades, including the World Health Organization (WHO),<sup>1–3</sup> United States Centers for Disease Control (CDC),<sup>4–6</sup> and Family Health International.<sup>7</sup> CDC has also published guidelines that are widely used in the evaluation of surveillance systems and provide a framework for assessing systems against a number of criteria, including but not limited to simplicity, accuracy, representativeness, timelessness, and acceptability (Box 6.1).<sup>4</sup> These criteria are important from a technical perspective, but the value of a surveillance system is ultimately judged by the extent to which it fulfils its objective of guiding programs and policy.<sup>1</sup>

#### Box 6.1 Examples of Key Surveillance Attributes

- Simple
- Accurate
- Representative
- Wide coverage
- Timely
- Respects privacy and confidentiality

### Information Collected by Surveillance Systems

HIV and STI surveillance provide routine information on key indicators that can guide the planning and evaluation of initiatives intended to reduce HIV and STI transmission. There are many different forms of information that may be of relevance to this task and a variety of ways in which such information might be collected. The prevention of HIV and STI transmission relies on a number of public health strategies, including education, distribution of condoms and clean needles, clinical services to diagnose and treat genital infections, and the provision of HIV testing.<sup>8</sup> These strategies have been endorsed by international organizations such as UNAIDS and WHO,<sup>8</sup> as well as many national governments. Their implementation can be monitored at several levels:

- *Process indicators* provide information on the extent to which each strategy is being implemented. At the most basic level, process indicators record funds allocated, numbers of staff employed, staff or units of prevention supplies distributed.<sup>9</sup>
- *Outcome indicators* are a second level of monitoring and look at the outcomes of the strategy, as would be illustrated by the proportion of people who regularly use condoms or HIV and STI knowledge and attitudes.<sup>9</sup>
- *Impact indicators* are the third and most important level of monitoring and focus on the impact of the strategy, as might be reflected in the number of new HIV and STI infections that are occurring in the population under surveillance.<sup>9,10</sup>

Ideally, information at all 3 levels should be available before, during, and after the implementation of a prevention strategy. The information collected prior to implementation can provide the basis for planning the implementation, while the information obtained during and after implementation allows the strategy to be evaluated in various ways.<sup>9</sup> It is important to note that a number of indicators are monitored on an ongoing basis by routine surveillance systems, and their measurement is not necessarily synchronized with the implementation of a specific prevention strategy.



Guidance on the construction of core indicators is described in various monitoring and evaluation documents.<sup>9,10</sup> These indicators will vary according to whether the country is considered to have a generalized or concentrated/low-prevalence epidemic as defined in the UNAIDS guidelines for second-generation surveillance.<sup>1</sup> In very early stages, when HIV infection is at low levels, it makes sense to focus attention on monitoring the potential transmission via surveys of sub-populations with risk behavior,<sup>1</sup> monitoring sexually transmissible infections (STIs) and other biological markers of risk,<sup>1</sup> tracking levels of testing to make sure that people at risk will be diagnosed if they acquire infection and routinely recording new diagnoses of HIV infection.<sup>1</sup> If transmission appears in particular population groups, such as injecting drug users or MSM, reflecting so-called “concentrated” epidemics, then it is necessary for HIV and behavioral surveillance systems to be put in place to allow the appropriate measurement of program indicators in these groups and populations to which they are epidemiologically linked. There may not need to be a strong focus on the wider population, although cross-sectional surveys of behavior in the general population and monitoring of HIV prevalence in populations such as antenatal women in urban areas could be conducted.<sup>1</sup> In so-called “generalized” epidemics, when the overall population prevalence exceeds 1%, broader surveillance measures are called for, which may involve monitoring of HIV prevalence in antenatal women on a routine basis in both urban and rural areas and cross-sectional surveys of behavior in the general population.<sup>1</sup> Depending on the nature of the epidemic, these activities may also be supplemented with the monitoring of populations at higher risk.<sup>1</sup> Data on morbidity and mortality are also important in generalized epidemics to provide an indication of overall public health outcomes.<sup>1</sup> Table 6.1 provides some examples of the 2006 national commitment and action indicators according to the HIV epidemic type.

**Table 6.1:** Examples of HIV/STI Prevention Program Indicators for Concentrated/Low-prevalence Countries<sup>10</sup>

Type of indicator	Concentrated/low-prevalence countries	Generalized epidemics
Process indicators	Percentage (most-at-risk populations) reached by prevention programs	Percentage of schools with teachers who have been trained in life-skills based HIV education and who taught it during the last academic year
Outcome indicators	Percentage of men reporting the use of a condom the last time they had anal sex with a male partner	Percentage of young women and men aged 15–24 reporting the use of a condom the last time they had sex with a nonmarital, noncohabiting sexual partner
Impact indicators	Percentage of (most-at-risk population(s)) who are HIV infected	Percentage of young women and men aged 15–24 who are HIV infected Percentage of infants born to HIV infected mothers who are infected

## Measurement of Outcome and Impact Indicators through Surveillance Systems

### TYPES OF SURVEILLANCE SYSTEMS

The indicators needed to monitor HIV and STI prevention initiatives can be obtained through routinely collected health information systems, or data collection systems that are put in place specifically for the purpose of monitoring. A third, hybrid approach involves supplementing routinely collected health information with additional data collection in designated areas of interest. In the following sections, the main surveillance approaches are described, and their relative strengths and weaknesses assessed.

### Routine Case-Reporting

The most widely used surveillance mechanism for infectious disease, including STI, HIV infection, and AIDS, is based on the routine reporting of newly diagnosed cases to a central public health unit, either by legal requirement or by agreement.<sup>1</sup> The case reporting may be conducted at a population level or in a more selective manner from specific health services or laboratories and cases can be reported either syndromically or etiologically based using a laboratory test (Box 6.2). The strengths and weaknesses of these different approaches are compared in Table 6.2.

Many countries have set up special structures for case-reporting.<sup>1</sup> Reporting of cases may either come from doctors or laboratories, or both, and the reporting can be centralized at various levels, depending on the administrative structure of the health service. This system has a natural appeal, in that it can be established on an ongoing basis, provides full geographic coverage, provides information about the presence of the virus in subpopulations, does not appear to involve substantial programmatic expense, and is used for advocacy.<sup>1</sup> The main indicator that can be routinely derived from systems of this kind is the number of new diagnoses over a defined time period. For each case, there is generally an expectation that information will be reported at least on age, sex, and area of residence.<sup>11</sup> This indicator depends very strongly on access to health services and the patterns of testing in a population; it has substantial limitations as an indicator of prevention programs,<sup>1</sup> particularly if it does not provide a denominator to be able to interpret surveillance trends.

### Population-Based Case Reporting

With the advent of tests for HIV antibody in 1984<sup>12</sup> a number of countries adopted HIV case reporting in the latter part of the 1980s.<sup>13–15</sup> In most developed countries, there is now generally a

#### Box 6.2 Examples of Case Reporting Surveillance Systems

- Population-based case reporting
- Selective case reporting
- Syndromic surveillance

**Table 6.2:** Strengths and Weaknesses of Case Reporting

	Population-based case reporting	Selective case reporting	STI syndromic surveillance
Strengths	<ul style="list-style-type: none"> <li>• Straightforward</li> <li>• Ongoing</li> <li>• Full geographic coverage</li> <li>• Provides information about subpopulations</li> <li>• Does not involve substantial programmatic expense</li> <li>• Useful for advocacy</li> <li>• Specific for the infection</li> </ul>	<ul style="list-style-type: none"> <li>• Provides information about populations at high risk of disease</li> <li>• High levels of reporting</li> <li>• Specific for the infection</li> </ul>	<ul style="list-style-type: none"> <li>• Does not require STI testing infrastructure</li> <li>• Cheap</li> </ul>
Weaknesses	<ul style="list-style-type: none"> <li>• Reliant on health seeking behavior and healthcare provider reporting</li> <li>• Suffers from underreporting, particularly in developed countries</li> <li>• May not detect epidemics in specific subpopulations</li> <li>• No testing denominator</li> </ul>	<ul style="list-style-type: none"> <li>• Only a subset of the populations</li> <li>• Reliant on health seeking behavior and healthcare provider reporting</li> <li>• May not detect epidemics in specific subpopulations</li> <li>• No testing denominator</li> </ul>	<ul style="list-style-type: none"> <li>• Nonspecific</li> <li>• Difficult to distinguish current from recurrent infections for some STIs</li> <li>• Poor sensitivity</li> <li>• No testing denominator</li> </ul>

high level of standardization in procedures used for HIV and STI case-reporting, as well as good levels of reporting.<sup>16,17</sup> However, several of the larger countries in Europe, notably Italy and Spain, still do not have national reporting of HIV diagnoses<sup>13</sup> and in the United States, a number of key states have taken some time to adopt HIV reporting.<sup>18</sup> Also in many countries, in the developing world, case reporting systems are not well respected, because they are subject to high degrees of underreporting or incomplete reporting.<sup>19</sup>

### Selective Case Reporting

Selective case reporting involves reporting from a sample of healthcare providers, usually thought to provide services for populations at high risk of diseases. For example in Europe, notification of gonorrhea and syphilis infections is mandatory for all physicians in most countries, whereas laboratory reporting or sentinel case reporting is more common for chlamydia.<sup>20</sup> Selective case reporting has a number of limitations. First, in many countries and even local areas considerable variations exist in clinical sites and the populations who use these services, making comparisons difficult between geographical areas.<sup>20</sup> Second, the coverage of the clinics may vary considerably affecting the representativeness of the reported data.<sup>20</sup> Third, some specialized sexual health clinical sites that attract high risk populations may report a higher proportion of gonorrhea and syphilis cases than genital chlamydial infections.<sup>20</sup> Finally, the lack of denominator data precludes the interpretation of time trends, particularly for chlamydia (Table 6.2).

### Syndromic Case Reporting

In the first years of the HIV epidemic, AIDS case reports provided the only basis for surveillance, and continued to do so on a global basis once HIV was discovered, as testing was not widely available, particularly in developing countries. The international monitoring of the global epidemic was based on AIDS case reports in those years, although there was a recognition that

underreporting of AIDS would be substantial in countries that could not systematically offer testing for HIV to people with suspected AIDS.<sup>21,22</sup> Reporting of AIDS case counts in a number of countries with good surveillance systems provided the basis for estimating past levels of HIV infection<sup>23,24</sup> through mathematical back-projection.<sup>25</sup> In developing countries, the syndromic AIDS case definition, that did not require confirmation of HIV status, was endorsed for surveillance purposes.<sup>26</sup> Until the mid 1990s, progression to AIDS was little modified by treatment, and generally resulted in serious illness and contact with the health system. From 1996 onwards, this situation changed, with the major improvements in therapy, such that AIDS no longer represented and irreversible late stage of HIV disease. AIDS-defining illnesses still arose in people who had access to treatment, but were generally recognized as being as consequence of poor adherence. As a result of the improvement in treatment, many countries saw a fall in the numbers of AIDS cases, with up to half now occurring in people presenting with HIV for the first time.<sup>27–29</sup> Such cases of late presentation indicate a failure of access to HIV testing, and should be tracked to inform public health policy.

In most developing countries, STI syndromic case reporting has formed the basis of STI surveillance for many years as STI tests were yet to be introduced and are still not widely used in all countries.<sup>21</sup> The key syndromes monitored are genital ulcer syndrome: nonvesicular and vesicular, urethral discharge syndrome, vaginal discharge syndrome, and lower abdominal pain in women.<sup>21</sup> STI syndromic case reports have important limitations. First, only genital ulcer disease (nonvesicular) usually represents recently acquired sexually transmitted infections, others syndromes such as vesicular ulcers may represent recurrent HSV infections. Second, most syndromes are quite nonspecific. Many other conditions (other than STIs) cause vaginal discharge and abdominal pain in women. Third, reporting is extremely incomplete because of the asymptomatic nature of many STIs.<sup>21</sup> A recent study in China demonstrated that using syndromic diagnosis identified <10% of positive cases compared to laboratory diagnosis.<sup>22</sup>

Some countries also monitor the syndromes associated with STIs. The example of chlamydia-related pelvic inflammatory disease illustrates the difficulties associated with monitoring of STI complications. The extent of morbidity from chlamydia-associated PID in most counties has been poorly assessed. Methods to measure the extent of PID vary considerably and have involved collation of data from primary healthcare clinics, extraction of data from hospital databases, case-control studies, special surveys, cohorts and data linkages studies. However, most of these assessments are not ongoing and would therefore not strictly fit the definition of surveillance. All these methods have strengths and weaknesses. Cohort studies, particularly those with data linkage components, are the most robust study design, but are associated with significant costs. Studies focused only on hospital settings are cheaper and more feasible but might overestimate progression rates as they include more severe cases. For all methods, the signs and symptoms of nature of PID and epididymitis are nonspecific, there are many causes of PID and an etiological role for *C. trachomatis* is not always definitive; a large proportion of women are only mildly symptomatic; and there is no simple and accurate diagnostic test currently available for diagnosis of PID. Laparoscopy is often used as a “gold standard” in PID diagnosis, but it cannot be practically used in primary care settings, where most cases of PID are managed.<sup>23</sup>

For example in Australia, data have been collated over the past 10 years through extraction of chlamydia-related reproductive outcomes from an annual surveys of general practitioners<sup>24</sup> and extraction of admission data from hospitals.<sup>25</sup> In both these assessments, information about previous chlamydia infections is lacking. In other countries, chlamydia-related reproductive outcomes have also been assessed through cohort studies and/or data linkage projects. For example, in Sweden a large retrospective population based cohort study (the Uppsala Women’s Cohort Study) provides estimates on severe reproductive tract complications associated with diagnosed genital chlamydial infection. Outcomes from the cohort are linked with laboratory, hospital, and population register to estimate the cumulative incidence of hospital diagnosed pelvic inflammatory disease, ectopic pregnancy, and infertility.<sup>23</sup>

### Box 6.3 Examples of Repeated Surveys

- Sentinel surveillance
- Regular behavioral surveillance
- Repeated surveys of HIV/STI prevalence

## Repeated Surveys

Recognizing the limitation of routine case-reporting, many countries have conducted surveys to support the planning and evaluation of HIV and STI prevention programs. The key feature of such surveys is that they obtain information on a defined population that would not arise in the course of routine health service delivery. The population involved in HIV-related surveys have generally been defined by either a behavioral characteristic, such as sexual or injecting activity, or a link to a defined setting such as a clinical service or institution that can be used as a site of recruitment to the survey.<sup>26</sup>

A wide variety of methodological approaches have been used for these surveys, including but not limited to sentinel surveillance of women attending antenatal clinics, cross-sectional surveys and population-based household surveys (Box 6.3).<sup>26–28</sup> The strengths and weaknesses of these different approaches are compared in Table 6.3. Specialized sampling methods such as respondent-driven sampling have also been traditionally used to access “hidden” populations.<sup>29,30</sup>

In the 1980s, when these surveys were first implemented, there was strong support in some countries for using so-called “anonymous unlinked” methods, which involved HIV testing of blood samples taken for other purposes without specific consent.<sup>31</sup> This approach was thought to provide more representative estimates of prevalence than would be obtained through consensual surveys,<sup>31</sup> but this has largely been discredited, because it is seen as depriving individuals of test information that could be to their benefit.<sup>31</sup> ANC sentinel surveillance has continued but now involves provision of results to patients. However, it has a few limitations; only pregnant women are tested, the reason for presentation (pregnancy) can be affected HIV infection, the patient profile may change over time, and the selected sites selected for surveillance may not be representative of the wider community.<sup>32</sup>

**Table 6.3:** Strengths and Weaknesses of Repeated Surveys

	ANC sentinel surveillance	Cross-sectional study	Population based household surveys
Strengths	<ul style="list-style-type: none"> <li>• Convenience sample</li> </ul>	<ul style="list-style-type: none"> <li>• Rich data source</li> <li>• Access to populations that may not attend health service</li> </ul>	<ul style="list-style-type: none"> <li>• Rich data source</li> <li>• Access to populations that may not attend health service</li> </ul>
Weaknesses	<ul style="list-style-type: none"> <li>• Deprives individuals of test information (anonymous unlinked systems only).</li> <li>• Often includes pregnant women only</li> <li>• Pregnancy rates are affected by HIV infection</li> <li>• Limited demographic and behavioral characteristics</li> <li>• Services may not be geographically representative</li> </ul>	<ul style="list-style-type: none"> <li>• Selection bias</li> <li>• Participation bias</li> <li>• May not be repeatable</li> <li>• Some methods are resource intensive</li> </ul>	<ul style="list-style-type: none"> <li>• Participation bias</li> <li>• Suited for generalized epidemics</li> <li>• Costly</li> <li>• Cannot track intermediate trends</li> </ul>



In recent years, there has been increasing use of household-based surveys that attempt to recruit representative samples of the population, especially in settings where HIV infection is believed to be generalized, with predominantly heterosexual transmission.<sup>28</sup> For some years there was a clear distinction between surveys that aimed to collect information primarily on HIV prevalence, either via blood or saliva specimens, and those that sought only behavioral or attitudinal information, but more recently there has been a trend towards integrating the two as far as possible.<sup>26,28</sup>

The integration of HIV testing into household-based surveys has provided greater information on the behavioral risk factors and the demographic and geographical patterns of HIV infection and has allowed ANC surveillance results to be calibrated.<sup>28</sup> On the other hand, the surveys are very costly and resource intensive and therefore only conducted about every 5 years, precluding the ability to track intermediate term trends.<sup>28</sup> Furthermore, participation can be an issue with major differences in the absence and refusal rates between women and men, between urban and rural areas, and between geographical.<sup>28</sup>

## Clinic-Based Surveillance

A key element of the response to the HIV epidemic in many countries has been the provision of HIV and STI testing through various clinical sites, either via pre-existing facilities such as sexual health clinics (Box 6.4), through the establishment of services specifically for the purpose of HIV counseling and testing.<sup>26,33</sup> These sites are often designed in ways that allow them to provide access to particular population groups who may otherwise be marginalized or stigmatized and therefore not attend mainstream health services.<sup>26,33</sup> The strengths and weaknesses of this approach is described in Table 6.4.

Clinical sites that provide HIV and STI testing therefore have the potential to report on several key indicators that may be of interest in program planning and evaluation.<sup>34</sup> The availability of denominator data is particularly useful, because it allows the number of positive HIV or STI tests to be interpreted in the light of testing patterns, providing a positivity rate that can be used as an indicator of the long-term outcome of prevention programs.

Routine testing data collated from clinical sites for the purposes of HIV monitoring and surveillance have been used in both generalized<sup>35–46</sup> and concentrated/low-level epidemics<sup>47–62</sup> for over 20 years. A recent paper by Baryarama et al., actually found that the HIV prevalence among asymptomatic clients

**Table 6.4:** Strengths and Weaknesses of Clinic-Based Surveillance Based on Routine Testing Data

	Clinic-based HIV/STI surveillance based on routine clinical data
Strengths	<ul style="list-style-type: none"> <li>• Rapid results</li> <li>• Minimal burden to sites</li> <li>• Access to high-risk groups</li> <li>• Can provide information on routinely collected risk behavior</li> <li>• Can be a proxy for prevalence if high testing rates</li> </ul>
Weaknesses	<ul style="list-style-type: none"> <li>• Select bias</li> <li>• People with established HIV infection will attend for HIV testing, so not a true reflection of prevalence (more a reflection of diagnosis rate)</li> <li>• May not be generalizable to wider population</li> </ul>

attending 8 standalone VCT sites across Uganda was similar to that in national HIV serosurvey data overall (10.1% and 9.7%, respectively).<sup>46</sup> However, in countries with high rates of testing and detection of infection, the positivity rates may not be a true reflection of prevalence but more an indicator of the rate of new diagnosis.<sup>46</sup> For example, in Australian diagnosis rates obtained from a clinic-based surveillance systems in Victoria have been reported at around 2% for men who have sex with men in the last few years,<sup>63</sup> whereas a recent prevalence study suggests the prevalence may be closer to 13%.<sup>64</sup>

In regards to STIs, surveillance systems based on routine testing data are being rolled out increasingly and proving useful in the interpretation of chlamydia passive surveillance trends. In the year 2000, a comprehensive surveillance system (called ASSIST) was introduced in the UK, which collates individual-level data about all laboratory tests for sexually transmitted infections carried routinely out in departments of GUM, the Avon Brook clinic, and the Health Protection Agency and trust laboratories.<sup>65</sup> The system demonstrated there was an increasing number of chlamydia positive tests being reported, which could be interpreted as being due to increased transmission; however chlamydia positivity rates in the area did not increase.<sup>65</sup>

On the other hand, in Australia, there was an increasing number of case reports of chlamydial infections notified; however chlamydia positivity rates in young heterosexual women aged less than 25 years, reported through the sexual health service network showed a significant increase between 2004 and 2008, from 10%–13%. These data from Australia suggest the rise in case reports may be related to increased transmission in the community.<sup>66</sup>

In clinical sites, where testing rates are high, the STI positivity rate may be reliably used a prevalence measure among the people attending the service.<sup>67</sup> Clinical sites are also in a position to provide information on risk behavior that is routinely obtained from clients<sup>33</sup> and can serve as an outcome indicator for prevention programs. The routine nature of the data also allow for rapid epidemiological assessment of populations affected and changes in the burden of disease.

### Box 6.4 Examples of Clinic-Based Surveillance Systems

- Screening for syphilis in antenatal women
- Testing of blood donors for HIV
- Examination for STIs among sex workers attending a special clinic
- Reports of risk behavior among students attending tertiary health services

The main methodological disadvantage of using indicators collected from routine practice at clinical sites is that they may be unrepresentative of populations in whom the program implementation is taking place.<sup>26</sup> Also unless there is a large network of services that cover the populations at risk, then there is the possibility of the system also being unrepresentative. For example, the paper by Baryarama et al. found that the VCT estimates were higher among rural VCT clients compared to rural serosurvey participants (8.2% and 5.2%, respectively) and the authors suggested the findings reflect of self-selection bias among rural VCT clients.<sup>46</sup> On the other hand, a number of populations of importance for HIV prevention cannot be reliably accessed in any other way,<sup>31</sup> and there is no reason to assume that indicators derived from routine clinical practice will be any less representative than those that are obtained by other means.

### MEASURING HIV INCIDENCE THROUGH SURVEILLANCE SYSTEMS

The central objective of HIV and STI prevention programs is to reduce the extent of transmission accordingly. Incident HIV infection rates are a key programmatic indicator as they reflect the rate of transmission<sup>68</sup> and help determine both the need for intervention programs and their effectiveness, but are very difficult to measure in practice. Direct measurement of incidence requires the use of repeat HIV/STI testing in the setting of cohort studies, which are not generally incorporated into routine surveillance systems as they are too expensive to be undertaken as ongoing population monitoring initiatives.<sup>68</sup> Prospective cohort studies are also complex, require long and costly follow-up and data are also subject to biases such as the Hawthorne effect.<sup>69</sup> Given the importance of HIV/STI incidence as an indicator, a number of alternative approaches have been used to provide HIV incidence estimates including repeat testing, specialized HIV serological assays and mathematical techniques

#### Box 6.5 Examples of Systems to Measure HIV/STI Incidence

- Repeat testing in a cohort
- Repeat testing in a clinical setting
- Prevalence of HIV infection in people whose first episode of drug injecting has been within the past year
- Specialized serological assays
- Mathematical techniques

(Box 6.5). The strengths and weaknesses of these different approaches are compared in Table 6.5.

The use of repeat-testing data is appealing for estimating HIV incidence for several reasons; it includes large sample sizes, demographic characteristics and risk behavior data are routinely recorded, includes high risk population, who may otherwise not participate in cohorts or other research.<sup>69</sup> However, the method has some weaknesses selection bias due to changes in the client profile or testing patterns over time and people may seek testing and treatment for infections outside the clinic that is being monitored.

The findings from prevalence surveys can be used to provide indirect estimates of incidence in people whose earliest exposure to HIV/STI infection can be assumed to have been relatively recent. For example, the prevalence of HIV infection in people whose first episode of drug injecting has been within the past year can be taken as a surrogate for 1-year incidence, provided other sources of infection are unlikely.<sup>70</sup> Studies in Africa have assessed trends in HIV incidence by analyzing the results of HIV prevalence among 15–24 year-old pregnant women.<sup>71</sup>

A major technical advance in surveillance over the past decade has been the development of serological assays that can be applied to single specimens to distinguish recently acquired HIV infections from those of longer duration.<sup>72</sup> These tests can be applied to specimens obtained either through routine case-reporting,<sup>73</sup> prevalence surveys,<sup>74</sup> or clinic-based surveillance,<sup>75–77</sup> and used as the basis for estimating incidence. Examples of

**Table 6.5:** Strengths and Weaknesses of Systems that Measure HIV Incidence

	Cohort	Repeat testing in a clinical setting	Serological assays	Mathematical techniques
Strengths	<ul style="list-style-type: none"> <li>• Direct measure</li> </ul>	<ul style="list-style-type: none"> <li>• Cheap</li> <li>• Data are widely available</li> <li>• Large sample sizes</li> <li>• Includes high risk f people</li> <li>• Long time periods</li> </ul>	<ul style="list-style-type: none"> <li>• Can be applied to a single specimen collected in a cross-sectional study</li> </ul>	<ul style="list-style-type: none"> <li>• Cheap</li> <li>• Calculation based on data from other studies</li> </ul>
Weaknesses	<ul style="list-style-type: none"> <li>• Expensive</li> <li>• Complex</li> <li>• Long follow-up</li> <li>• Differential loss to follow-up</li> <li>• Hawthorne effect</li> </ul>	<ul style="list-style-type: none"> <li>• Indirect measure</li> <li>• Reliant of frequent testing behavior</li> <li>• Results require continual revision with subsequent years of data</li> </ul>	<ul style="list-style-type: none"> <li>• Indirect measure</li> <li>• Cross sectional sample–selection bias</li> <li>• Can misclassify AIDS cases and people in ARV treatment</li> <li>• Involves complex mathematical calculations</li> <li>• Requires an appropriate definition of the population the incidence is estimated for</li> </ul>	<ul style="list-style-type: none"> <li>• Indirect measure</li> <li>• More accurate in the early years of the HIV/AIDS epidemic</li> </ul>



the public health application of these assays have been studies involving attendees at anonymous testing clinics,<sup>69,77</sup> sexually transmitted disease clinics,<sup>75–77</sup> and injecting drug users attending treatment services.<sup>78–80</sup>

A number of public health agencies are already using these tests on a routine basis. Currently, HIV incidence assays have been incorporated into national HIV incidence surveillance in the USA<sup>81</sup> and increasingly in Europe. In Africa, 15 of 44 sub-Saharan African countries report HIV incidence estimates and HIV incidence assays have comprised 20% of these estimates since 2006.<sup>82</sup>

Despite this, there is not yet a consensus on their ideal means of application, and particular debates about the validity of the resulting estimates of HIV incidence.<sup>74,83</sup> Guidelines are currently being prepared by the World Health Organization that contains advice on the recommended validation strategies and ideal ways to use the assays in routine surveillance.

## Surveillance for Drug Resistance

Given the importance of providing the correct treatment for STIs and HIV, many countries have implemented gonococcal antimicrobial resistance surveillance programs; some systems have been in place for 10–20 years. More recently a number of countries have introduced HIV drug resistance surveillance (Box 6.6). The strengths and weaknesses of these different approaches are compared in Table 6.6.

## HIV Resistance Surveillance

Surveillance for transmitted drug resistance has become a routine HIV surveillance activity in a number of countries including France, Canada, Australia, and others.<sup>66,84,85</sup> At the population level, information about the occurrence of transmitted drug resistance and its time trends and distribution in the population, can guide overall treatment policy, particularly in regard to

preferred first line therapeutic options. In some regions of the world, if the proportion of resistance in this population reaches a specified level (e.g., 5% or 10%), routine drug resistance testing may be recommended for all persons known or assumed to be recently infected with HIV who are newly diagnosed or who are beginning HIV treatment.<sup>84</sup>

The World Health recommends that the surveillance of drug resistance in newly diagnosed persons with HIV should not be initiated until there is an indication that the level of transmitted resistance in the country may be at or above 5%, but planning should take place before that point, including threshold resistance surveys. WHO recommends that if the surveys detect HIV strains containing major mutations associated with resistance in 2 successive years, then surveillance should be considered. The threshold surveys can also provide the opportunity for testing methodology and evaluating potential sentinel surveillance sites.<sup>84</sup>

The surveillance systems can focus on all new diagnosis or only those that are identified as recently acquired. Each of these approaches have strengths and weaknesses. Annual monitoring of target groups representative of persons recently infected with HIV provides the best estimate of trends in drug resistant HIV transmission. Specimens from the recently infected provide important information about the transmission of mutations associated with new drugs and provide a direct estimate of the incidence of transmitted resistance. This is the current situation in Australia, where HIV surveillance captures a person's past testing history enabling newly acquired infections to be easily identified and account for about 30% of diagnoses.<sup>85</sup> However, this approach is not usually practical in resource-limited countries. Newly infected individuals are often difficult to identify in many countries; the majority of individuals with HIV are not diagnosed until late in their clinical course, when disease develops.<sup>84</sup>

HIV drug resistance surveillance focused on newly diagnosed HIV infections is more commonly conducted as such populations are generally accessible. Newly diagnosed HIV infections generally represent new patients likely to be evaluated for treatment by a clinician and can provide helpful information about mutations that remain detectable years after infections. By focusing on newly diagnosed infections the prevalence of HIV drug resistance prevalence is unlikely to relate to a certain time period but the

### Box 6.6 Examples of Systems to Measure HIV and STI Drug Resistance

- HIV antiretroviral therapy resistance surveillance
- Gonorrhea antimicrobial resistance surveillance

**Table 6.6:** Strengths and Weaknesses of Drug Resistance Surveillance

	HIV drug resistance surveillance—newly acquired infections	HIV drug resistance surveillance—new diagnoses	Gonorrhea antimicrobial resistance surveillance
Strengths	<ul style="list-style-type: none"> <li>• Best indicator of whether mutations associated with new drugs is being transmitted</li> <li>• Enables trends to be assessed over time</li> </ul>	<ul style="list-style-type: none"> <li>• More accessible populations</li> <li>• The total numbers of newly diagnosed individuals are often known</li> </ul>	<ul style="list-style-type: none"> <li>• Most countries with laboratory infrastructure can undertake AMR surveillance</li> </ul>
Weaknesses	<ul style="list-style-type: none"> <li>• Newly infected individuals are often difficult to identify in many countries</li> </ul>	<ul style="list-style-type: none"> <li>• Does not reflect transmitted resistance within a certain time period</li> <li>• Proportions of recently infected persons may change from year to year that could affect trends</li> </ul>	<ul style="list-style-type: none"> <li>• Sensitivity</li> <li>• Representativeness</li> </ul>

incidence of transmitted resistance can be estimated from the subset of recently infected persons in the population. The main limitation of monitoring newly diagnosed infections is that over time there could be changes in the proportions of recently and established infections in the sample, which could bias trends in resistance.<sup>84</sup>

### Gonorrhea Antimicrobial Resistance (AMR)

AMR surveillance is crucial to inform treatment options as it is well established that once resistance to an antibiotic has reached a level of 5% or more, the antibiotic should be removed from treatment schedules for gonorrhea infection.<sup>85</sup> Unlike other bacterial STIs, *Neisseria gonorrhoeae* has a particular capacity to become resistant to antibiotics leading to the removal of penicillins, tetracyclines, and now quinolones from the treatment schedule in many countries.<sup>85</sup>

Surveillance for AMR is common in many countries including Australia, the United Kingdom (UK), United States (US), Sweden, South Africa, and recently Russia.<sup>85</sup> There are also regional programs including the WHO WPR and South-East Asia Regions (SEAR), Gonococcal Surveillance Programmes (GASP) and a program in the European Union. However in many countries and regions AMR surveillance is absent such as in Canada, Malaysia, America, and Africa.<sup>85</sup>

The surveillance methods employed across countries vary. For example in the UK, isolates collected from patients attending sentinel sites over a 3-month period are assessed. Whereas in the US, the program involves assessment of specimens from male patients in 25 sentinel sites each month. Further to this, in Australia, the US, and the UK, MIC-based methods are used to assess resistance, whereas the WPR GASP uses a number of methods including disk diffusion.<sup>85</sup>

Similar to issues faced by other sentinel surveillance programs, AMR often suffers from representativeness issues as in many countries it is difficult to define an appropriate sentinel population that can provide sufficient samples to present all populations at risk of gonorrhea.<sup>86</sup>

### Choice of Surveillance Systems

Given the variety of options for surveillance, all with individual strengths and weaknesses, it is perhaps unsurprising that virtually all countries, and to some extent different jurisdictions within countries, have come up with their own combinations of methods to measure key indicators of HIV prevention initiatives.<sup>87</sup> Surveillance systems are never perfect and vary considerably according to the area of public health being monitored, the available resources, and factors such as the structure of the health system in which it is operating and sociocultural factors. Furthermore, it is difficult to assert in any absolute sense that one system or set of systems is clearly superior to another.

Nevertheless, there are some criteria that have emerged for guiding the choice of system. Governments and their partners in HIV prevention take these criteria into consideration in determining ideal strategies for the populations that fall under

their responsibility. At a practical level, the surveillance system must fit within the budget and structure of the overall health system at any given time. There is no point in countries designing systems that are not properly resourced, nor should they try to put in place surveillance mechanisms that create tensions with service provision. Similarly, there may be political or cultural constraints that have an impact on the methodological options available for surveillance systems.

From a scientific and public health perspective, it is clear that HIV epidemics can differ considerably over place and time, and the monitoring systems that are used to guide prevention initiatives need to reflect the current state of the epidemic in a given setting.<sup>1</sup> In any country experiencing an HIV/AIDS epidemic, the relationship between prevalence and incidence, and the behavioral and demographic profiles of already-infected versus at-risk individuals, changes over time as the epidemic becomes more established in the population. The ongoing challenge for surveillance systems, whether they are related to HIV infection or any other condition, is to be sufficiently stable to allow valid comparisons to be made over time, at the same time as being responsive and adaptable to an evolving environment, should the patterns of infection start to qualitatively change.<sup>1</sup>

#### Summary

The most widely used surveillance mechanism for monitoring HIV/STIs is based on the routine reporting of newly diagnosed cases to a central public health unit. Selective case reporting also occurs in some countries and involves reporting from a sample of healthcare facilities providing services for populations at high risk of diseases. In most developing countries, STI syndromic case reporting has formed the basis of STI surveillance for many years as STI tests were yet to be introduced and are still not widely used in all countries. Recognizing the limitation of routine case-reporting, many countries have conducted behavioral and biological surveys to support the planning and evaluation of HIV and STI prevention programs. A wide variety of methodological approaches have been used for these surveys, including sentinel surveillance of women attending antenatal clinics, cross-sectional surveys, and population-based households surveys. A number of approaches have been used to provide HIV incidence estimates including repeat testing, specialized HIV serological assays, and mathematical techniques. Surveillance for HIV drug resistance and gonorrhoea antimicrobial resistance has become a routine surveillance activity in many countries. The chapter discusses strengths and weaknesses of all these systems, and criteria for guiding the choice of system in a country.

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# Epidemiological Interactions between HIV-1 and other STI: A Complex, Continuing Narrative

# 7

Brian P. Mulhall

## Early Studies

Not long after the first published description of AIDS<sup>1</sup> and the discovery of its cause, the human immunodeficiency virus (HIV),<sup>2,3</sup> studies in men who have sex with men (MSM)\* suggested an association with sexual behavior and STI,<sup>4-12</sup> but deficiencies in study design<sup>13</sup> hampered definite conclusions. For the next 15 years or so, little further research was undertaken in MSM regarding associations with STI; resources were instead directed toward effective treatments of HIV-infected individuals with antiretroviral drugs (ARV). In the last decade, there has been a resurgence of interest in studies of homosexual/MSM that have concentrated instead on the effect that STI have on the infectiousness of HIV-infected MSM. These will be reviewed later in this chapter.

From similar beginnings, reports from Africa and elsewhere showed that HIV was also transmitted during heterosexual intercourse, overshadowing the MSM epidemic; additionally, cross-sectional studies<sup>14-16</sup> suggested that genital ulcer disease (GUD) facilitated transmission of HIV. The evidence was stronger in those studies that were prospective,<sup>17-19</sup> with odds ratios that ranged from 2–4 times for GUD, and less for non-GUD.

In 1991, a landmark paper by Judith Wasserheit,<sup>20</sup> examining the potential interrelationships between HIV and other STI, coined a new concept, “epidemiological synergy”, by which was meant that each infection could amplify the other. Three mechanisms were suggested:

1. Increased transmission of HIV in the presence of other STI
2. Accelerated progression of HIV disease in the presence of STI
3. Alteration in the natural history, diagnosis, or response to therapy of other STI in the presence of HIV infection.

The last proposition is dealt with in Chapter 84 by Veerakathy Harindra, and the second will be reviewed only briefly owing to

paucity of evidence; therefore, the majority of this chapter will deal with the first proposition.<sup>1</sup>

In theory, increased transmission could occur as a result of:

- (a) Increased acquisition of HIV in the presence of STI, perhaps by disruption of mucosal integrity, or by a concentration of inflammatory cells in the presence of STI, some of which would be permissive for HIV infection, or
- (b) Increased shedding of HIV in genital secretions, due to an increased viral load in the presence of infection, in this instance by another STI.

## Establishing Epidemiological Synergy

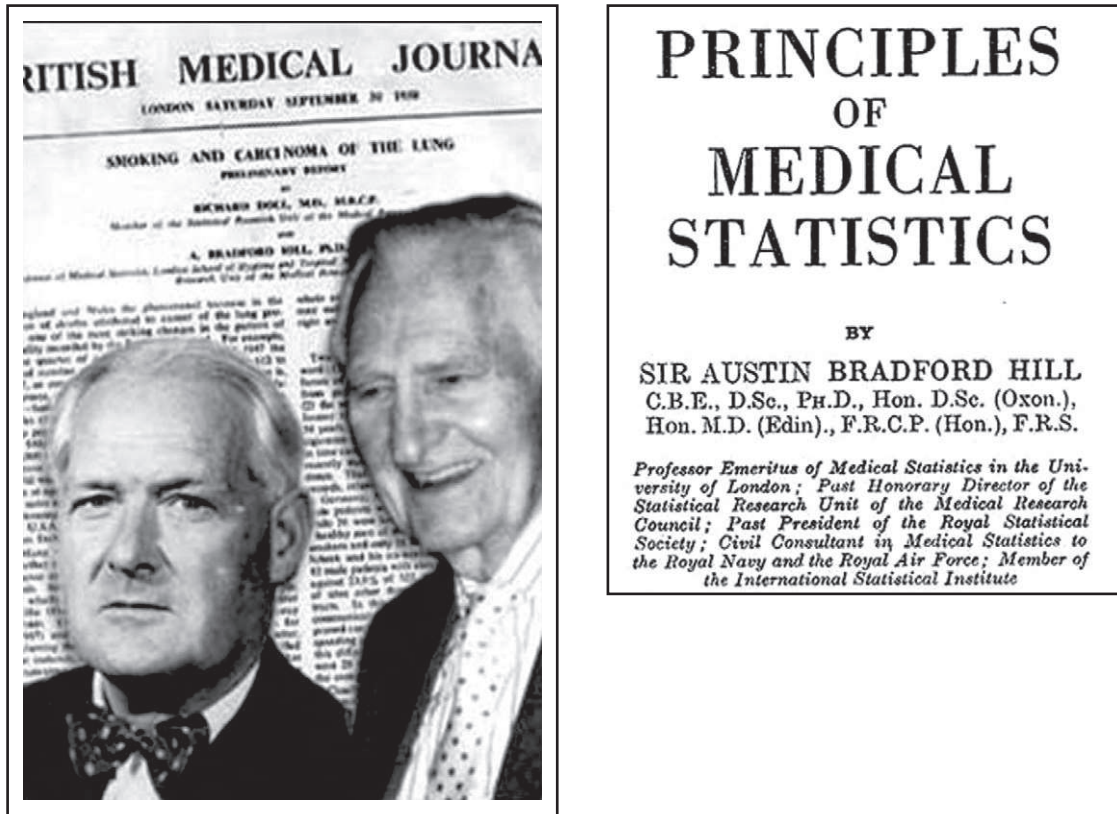
Despite a number of studies suggesting an association, there were obstacles to establishing a causal role for STI. The most obvious was the confounding variable of sexual behavior, which was associated with the exposure variable (STI) as well as the outcome of interest (HIV). In addition, any sample of persons studied might not provide true information about the relationship between exposure and outcome with respect either to the relationship that the sample actually displayed (selection bias), or apparently displayed (classification bias). In practice, epidemiologists attempt to do sufficient studies in diverse settings, thus limiting random error, systematic error (bias), and logical error (confounding).

In assessing the causal nature of an observed association, the Bradford Hill “criteria”, (he called them “considerations”), first published 45 years ago,<sup>21-23</sup> have long provided a background framework, akin to Koch’s postulates (Fig. 7.1 and Box 7.1).

In practice, it is difficult to establish a pure association of exposure (STI) and health outcome (HIV)-free from bias, confounding, and interaction with other exposures. The research situations in which this can occur are limited mainly to clinical trials, and perhaps large observational studies with impeccable design and execution. In the present context, epidemiologists

\*MSM (men who have sex with men) is a term that includes all men with significant same-sex sexual behaviors; it includes men who self-identify as homosexual, gay, or bisexual, as well as those who do not. The early studies referred to here were mainly in the former group.





**Fig. 7.1:** Sir Austin Bradford Hill (right), the father of medical statistics, seen here with Sir Richard Doll in 1950; in background their article on smoking.

#### Box 7.1 Bradford Hill Criteria for Causality

- Strength
- Consistency
- Specificity
- Temporality
- The only requirement, that is, for the exposure (STI) to precede the effect (HIV)
- Biological gradient
- Biologic plausibility
- Coherence
- Analogy
- Experiment

The strongest evidence for causality. Do preventative actions taken on the basis of a demonstrated cause and effect association alter the frequency of the outcome?

extended their horizons to encompass the domains of population-level relationships not reducible to studies of individuals. It should, however, be noted that neither observational nor treatment studies are able to easily separate the effects of STI on the infectiousness of HIV from their effects on HIV acquisition.

### Randomized Controlled Trials of STI to Prevent HIV

There have been six randomized controlled trials (RCTs) for bacterial STI, all in Africa,<sup>24,28–32</sup> and two for herpes genitalis.<sup>105,106</sup>

Results for the first three have been subjected to intense scrutiny for over 10 years. All used communities, rather than individuals, as the unit of randomization; for the first three, considered prototypes, the protocols can be summarized as follows in Box 7.2.

The results from Mwanza were published first<sup>24</sup> and showed a remarkable reduction in HIV incidence of 48% (Estimated RR 0.58, 95% CI 0.42–0.79,  $p = 0.007$ ).

It is easy, in retrospect, to understand the jubilation that accompanied this news in the scientific literature,<sup>25,26</sup> including

#### Box 7.2 Protocols and Results on HIV Incidence for the First 3 Intervention Trials in Africa

- A. Mwanza, Tanzania, 1991–1995. Intervention—improved STI treatment protocols via syndromic management in 6 communities, versus delayed intervention in 6 matched communities, total  $n = 12,537$  individuals.  
48% reduction in HIV (RR 0.58, 95% CI 0.42–0.79)
- B. Rakai, Uganda, 1994–1998. Intervention—mass STD treatment at 10-monthly intervals, versus placebo (vitamins and antihelminthic treatment). Ten community clusters, randomized, total  $n = 12,726$  individuals.  
No effect on HIV (RR 0.97, 95% CI 0.81–1.16)
- C. Masaka, Uganda, 1995–2001. Three intervention arms—behavioral (A), syndromic treatment (B), and routine community development activities (C). 18 rural communities were chosen, with a total population of about 96,000. No effect on HIV. The incidence rate ratios were (A) 0.94 (95% CI 0.60–1.45), (B) 1.24 (95% CI 1.02–1.56), (C) 1.0

the claim that Bradford Hill's criteria for causality had now been definitively established; however, this was only on the basis of the Mwanza experiment.<sup>27</sup>

It was some time before the Rakai and Masaka results were available, and to general dismay, neither showed any effect on HIV incidence.<sup>28,29</sup>

In Rakai incidence of HIV was 1.5 per 100 person years in both arms (RR 0.97, 0.81–1.16), with a significant decrease only in syphilis (RR 0.80, 0.71–0.89), and trichomoniasis (RR 0.59, 0.38–0.91).

In Masaka, there were no significant differences on any measure between the three arms.

The fourth trial, again flat (null) for HIV,<sup>30</sup> will be discussed in the section on periodic presumptive treatment (PPT); the last two, both null<sup>31,32</sup> have not been the subject of significant comment or debate in the literature.

In contrast, a large number of papers have been published over an extended period of time, reflecting the degree of concern over the perplexing, contrasting, and seemingly contradictory results of the three prototype trials.<sup>33–40</sup> Some of the explanations advanced are listed in the Box 7.3.

In the previous section on association and causality, it was stated that research situations free from bias and confounding are rare. They are limited mostly to clinical trials, and we have seen that the trials above were certainly not free from bias or confounding. Another kind of study that attempts to minimize epidemiological noise is a large observational study with impeccable design and execution.

One such study has been conducted in Africa, popularly known as the Four Cities study. The HIV epidemic shows considerable heterogeneity within sub-Saharan Africa. The multicenter study of factors determining the different prevalences of HIV in sub-Saharan Africa was designed to assess whether differences in characteristics of sexual behavior and/or factors affecting the probability of HIV transmission such as male circumcision or STI could explain the much more severe epidemics observed in East Africa than in West Africa. This cross-sectional, population-based study sampled about 1,000 men and 1,000 women in each of 2 cities with relatively low HIV prevalence (Cotonou, Benin; and

Yaounde, Cameroon) and 2 cities with high prevalence (Kisumu, Kenya; and Ndola, Zambia).<sup>41</sup>

The study found that some biological factors for HIV transmission differed between the high and low prevalence cities. In the cities with low prevalence, virtually all the males were circumcised, whereas in the cities with high prevalence, rates of circumcision were low—28% in Kisumu and 10% in Ndola. In addition, the prevalence of herpes type 2 (HSV-2) was higher among young women and men in the East African cities than in the West African cities. The study also identified some important differences in reported sexual behavior between the four populations including younger age at first intercourse and marriage in East Africa than in West Africa and larger age differences between spouses in East Africa. On the other hand, other characteristics of sexual risk behavior such as reported partner change rates and having had sex with a sex worker were more prevalent in the cities with low prevalence than in the cities with high prevalence. Hence, an important hypothesis raised by the study was that differences in risky sexual behavior could be outweighed by differences in biological cofactors that unduly influence HIV transmission, such as male circumcision and other STI, especially HSV-2.<sup>42</sup>

## Systematic Review of Data

In 2001 a systematic review,<sup>43</sup> of the large body of work accumulated thus far measuring the associations between STI and HIV, concluded that (assuming that confounding and publication biases were eliminated successfully) GUDs increase male susceptibility approximately 4 times, and female susceptibility 3 times, whereas non-GUD increase male susceptibility 3 times and female susceptibility 2 times. There also appeared to be a 2 times increase in the infectiousness of HIV sources with an STD, although data were very sparse for women with a non-GUD.

## Syndromic Treatment, Mass Treatment, Core-Theory, and Periodic Presumptive Treatment

We have seen that syndromic treatment of STI to reduce HIV was effective in the context of a clinical trial. Elsewhere, however, asymptomatic STI cannot (by definition) be treated within the syndromic paradigm, and together with other operational considerations, reduce its efficacy.<sup>44</sup> Moreover, mass treatment cannot achieve full coverage, and even if it could, would be too costly.

Therefore, a third approach has been trialled; it is currently known as periodic presumptive treatment (PPT), and relies heavily on “core-theory”, an introduction to which is now introduced as essential background information.

Yorke and colleagues studied the effects of a 1972 screening program for gonorrhea in asymptomatic women in the USA,<sup>45</sup> trying different models against seasonal oscillations of positive results. They showed that the “infecter number”—the average number of susceptible persons infected per infected index case during his or her infectious period—must exceed one for the

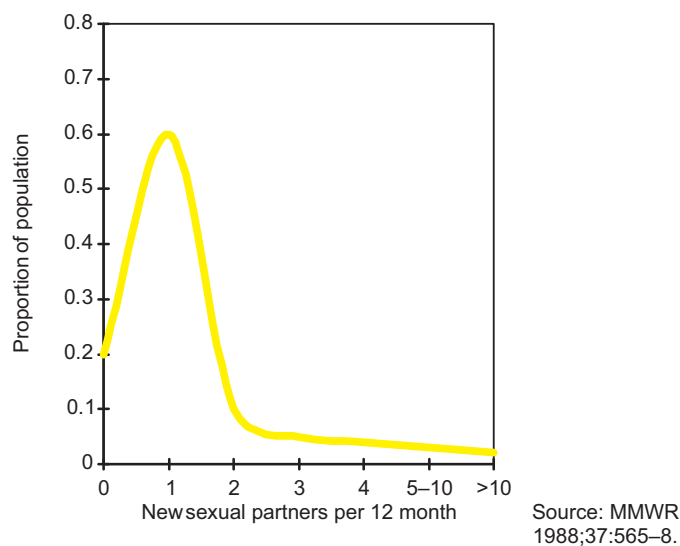
### Box 7.3 Possible Reasons to Explain Discrepancies between the First 3 Trials in Africa

- Curable STI may play a more important role in an early HIV epidemic (Mwanza, HIV prevalence 6%), versus a mature HIV epidemic (Rakai, HIV prevalence 16%)
- Suboptimal measurement of STI in Mwanza
- Suboptimal coverage in Rakai, including the possibility of reinfections
- Symptomatic STI (Mwanza) may be greater cofactors than asymptomatic STI (Rakai)
- There were lower rates of curable STI in Rakai, owing to lower risk behaviors
- The population attributable fraction (PAF) of STI to HIV may differ between populations
- The near impossibility of fully resolving the spurious effect of confounding sexual behaviors, particularly in the unknown partners of study participants

disease to be at an endemic equilibrium. The infected population would be closed by a saturation effect if there was acquired immunity, or by a pre-emption effect (already infected) if there was no such immunity (as in gonorrhea). Groups having a high prevalence, e.g. 20%, had substantial pre-emption effects, and formed a reservoir, or core-group.

In 1987–1988, only a few years after AIDS was first described, Robert May and Roy Anderson, using remarkably prescient estimates of the incubation period for AIDS, among other assumptions, brilliantly developed a simple model to describe the infector number, or “reproductive rate” for HIV, and indeed, most infectious agents, including STI.<sup>46,47</sup> Essentially, they showed that the potential for spread within a specific risk group depends on the magnitude of the basic reproductive rate ( $R_0$ ).  $R_0$  measures the number of infections produced, on average, by an infected individual in the early stages of an epidemic, when virtually all contacts are susceptible. As such, it depends on the average probability,  $\beta$ , that an infected individual will infect a susceptible partner, times the rate of partner change,  $c$  (within the specified risk category), times the average duration of infectiousness,  $D$ ; thus  $R_0 = \beta c x D$ .  $R_0$  must  $>1$  for an infection to be sustained, and to be an ecologic success.

Discussing this further, Brunham and Plummer<sup>48</sup> add that great heterogeneity in sexual behavior exists at the population level, with only a subset maintaining high rates of partner change. When rates of partner change per unit time are plotted from a random sample of an entire population, the distribution is nonnormal<sup>49</sup> (Fig. 7.2). A long tail of individuals who have high rates of new partner acquisition is observed. These individuals who have a high prevalence and incidence of STI, act as a reservoir of infection, and are the source of infection to others. They are termed core-groups, or high transmitters of STI.



**Fig. 7.2:** When rates of partner change per unit time are plotted from a random sample of an entire population, a long tail of individuals who have high rates of new partner acquisition is observed.<sup>49</sup>

The core-group concept has immediate and profound implications for STI control. If core-group members are kept free of infection, STI will gradually disappear.<sup>50</sup>

Thus, the concept of epidemiologic/targeted mass treatment of core-groups was developed,<sup>51</sup> and then tested in a group of female sex worker (FSW) and their clients in 1996–1997 in a mining town in South Africa.<sup>52</sup> High-risk women attended a clinic monthly, and were treated presumptively with a directly observed dose of 1g azithromycin. During the first 9 months of the intervention, the prevalence of gonorrhea and/or chlamydia fell from 24.9% to 12.3% within the first month; there was also a decline in GUD from 9.7% to 4.4%. In the client population (miners), the analogous figures were 10.9% and 6.2% at 6 months, and 5.8% to 1.3% for GUD.

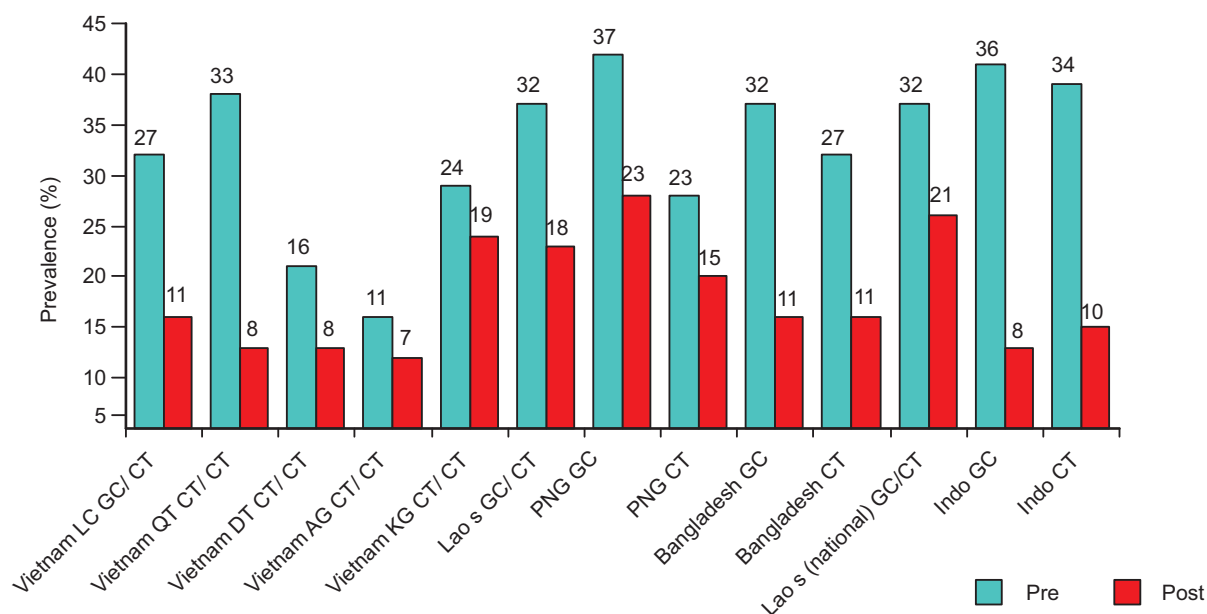
A similar intervention was instituted for FSWs in a slum area of Nairobi between 1998 and 2002, using monthly azithromycin.<sup>53</sup> This was additionally, an RCT for HIV prevention (the fourth in Africa); 466 HIV-negative FSWs were randomly assigned to drug or placebo, the primary study end-point was incidence of HIV. The results at 2 years showed a significant reduction in gonorrhea (RR 0.46, 95% CI 0.31–0.68) and Chlamydia (RR 0.38, 95% CI 0.26–0.57), but not in HIV (RR 1.2, 95% CI 0.6–2.5). The authors suggested that prevalent HSV-2 infection may have been an important cofactor; however, others have pointed out that the prevalence of HIV and GUD (especially chancroid) had already fallen to low levels in this population.<sup>54</sup> A very interesting finding in this study was the strong association between HIV incidence and a recently acquired STI, raising the possibility that STI may facilitate HIV transmission via increased infectivity of a coinfecting partner.

There followed other documented successes of PPT in various other populations and under differing operational circumstances,<sup>55–57</sup> and in September 2005, WHO convened a meeting in London to consider experiences with PPT, and to issue recommendations.<sup>58</sup>

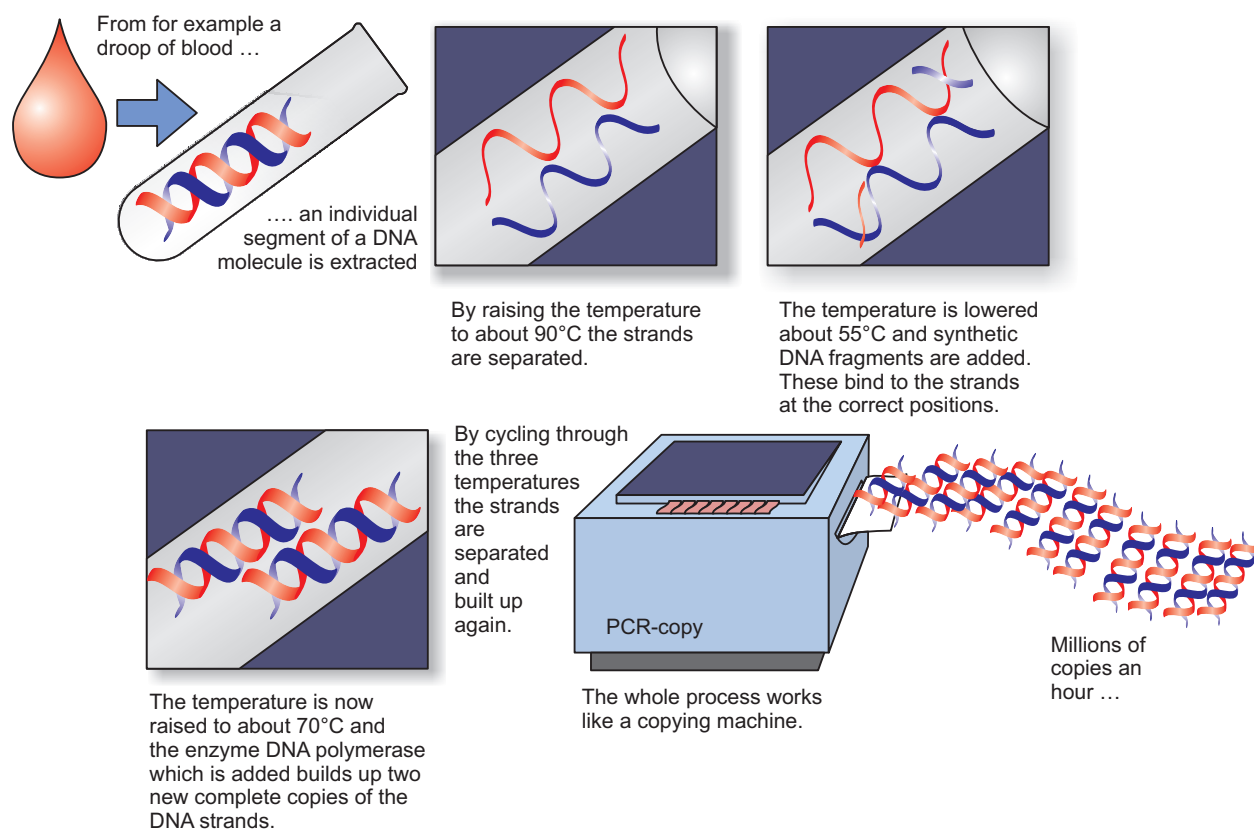
The principal determinants of success for PPT depend on individual circumstances that include a high proportion of curative STI, and how closely these are linked to core-groups, e.g. FSWs. They should probably be best considered as a temporary intervention to rapidly reduce rates of STI in populations with limited access to health services. Treatment of the FSWs regular sexual partners is also important. They are not a magic bullet, and operational issues remain, including optimal frequencies, anxieties regarding antibiotic resistance to gonorrhea, cost, and possible disincentives to condom use. Nevertheless, they have been used successfully in many different populations (Fig. 7.3). Their contribution to HIV prevention remains unknown.

## Influence of Stage of HIV and Other STI on HIV Viral Load

The application of the polymerase chain reaction (PCR) (Fig. 7.4) to HIV in plasma and other body fluids shed new light on the dynamics of HIV and enabled the number of viral particles (“viral load”) to be determined at any stage of HIV-1 infection.<sup>59–64</sup>

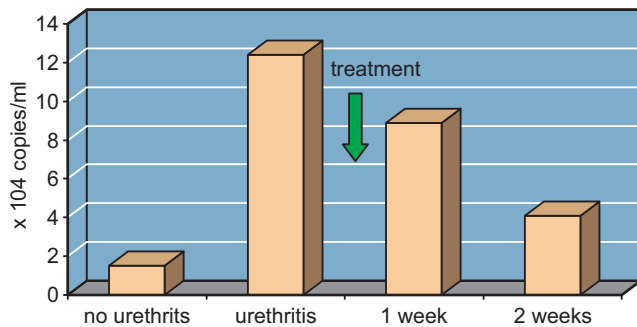


**Fig. 7.3:** Impact of PPT on GC and CT among female sex workers in Asia and Pacific, 2002–2009. *Source:* Bruce E, Australasian Sexual Health Conference 2008; McCormick D, FHI 2007; CHAS Lao PDR 2008; Bollen LJM et al., *Sex Transm Infect* 2010;86:61–5; and Graham Neilsen, FHI 2010 (reproduced with permission).



**Fig. 7.4:** Advances in Technology. Polymerase chain reaction.



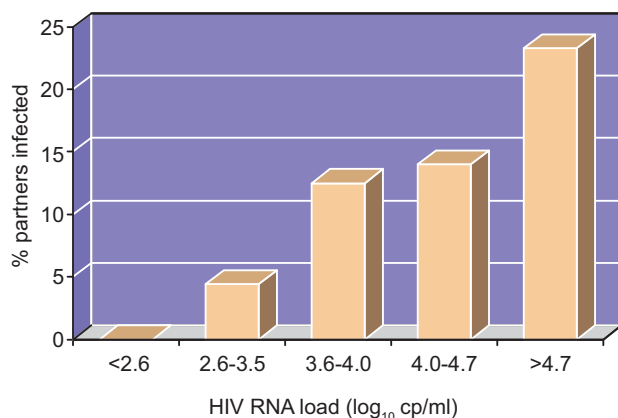


**Fig. 7.5:** Median concentration of HIV-1 in semen among 135 HIV-infected men in Malawi with and without urethritis.<sup>68</sup> Cohen et al. *Lancet* 1997;349:1868–73 (reproduced with permission).

Preliminary studies in Nairobi and elsewhere<sup>65,66</sup> demonstrated fluctuations of HIV in semen associated with urethritis. In Malawi, using a new assay,<sup>67</sup> Cohen and colleagues demonstrated in 1997<sup>68</sup> that HIV-shedding in semen was 8 times greater in HIV-positive men with urethritis ( $12.4 \times 10^4$  copies/ml) than in a control group of HIV-positive men without urethritis ( $1.54 \times 10^4$  copies/ml), despite similar CD4 counts and plasma viral loads. Gonorrhea was associated with the greatest concentration of HIV. Moreover, after the urethritis patients received antimicrobial therapy, the concentration of HIV in semen decreased to  $8.91 \times 10^4$ /ml at 1 week and  $4.12 \times 10^4$ /ml at 2 weeks (Fig. 7.5). The concentrations in plasma were unchanged. These were important observations because during sexual transmission of HIV, the relevant secretion is likely to be semen or cervical fluid, with blood levels a surrogate marker.

Nonetheless, a landmark study in 2000 demonstrated that plasma viral load was the chief predictor of heterosexual transmission of HIV<sup>69</sup> (Fig. 7.6).

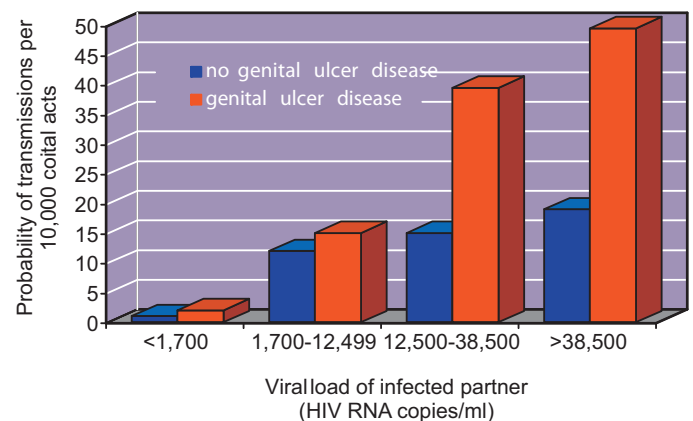
The Rakai trial data<sup>28</sup> identified 415 couples in which one partner was HIV-positive, and one was initially negative; 90 of



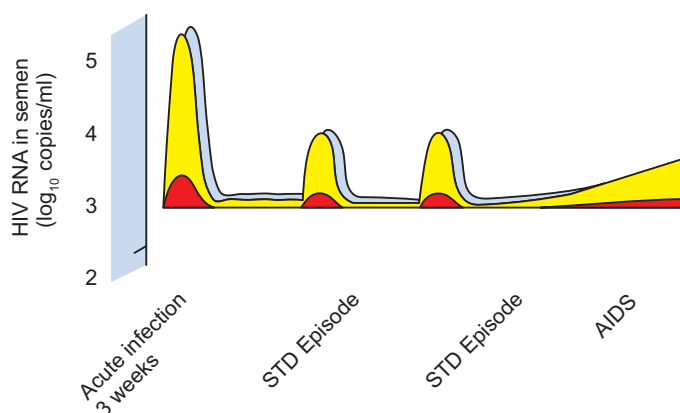
**Fig. 7.6:** Viral load and HIV-1 transmission.<sup>69</sup> Quinn TC et al., *N Engl J Med* 2000;342:921–9 (reproduced with permission).

the 415 initially HIV-negative partners seroconverted. The rate of male-to-female transmission was not significantly different from the rate of female-to-male transmission. The mean serum HIV RNA level was significantly higher among HIV-positive subjects whose partners seroconverted than among those whose partners did not seroconvert. There were no instances of transmission among the 51 subjects with serum RNA less than 1,500 copies/ml. They found a dose-response effect; the rate of transmission increased from 2.2 per 100 person-years to 23.0 per 100 person-years as the serum HIV RNA level increased from less than 3,500 copies/ml. Each log increase in viral load was associated with an increase, by a factor of 2.45, in the risk of transmission. Apart from previous studies on mother-to-child transmission this was the first (and remains the best) study of heterosexual risk of transmission. In a subsequent analysis of the same cohort,<sup>70</sup> 174 monogamous couples were identified, and the probability of transmission per coital act estimated from frequency of sexual intercourse. The probability of transmission increased from 0.0001 with a plasma viral load <1700 copies/ml to 0.0023 at >38000/ml; in addition, there was a significant increase at all viral loads if there was a history of genital ulceration (0.0041 vs 0.0011,  $p = 0.02$ ) (Fig. 7.7).

Meanwhile, in Malawi, Cohen's group showed, for the first time, that during "acute HIV" infection (best described as the period between infection with HIV and the appearance of antibodies routinely used to diagnose infection), the peak serum HIV load was extremely high, often >1 million copies/ml.<sup>71,72</sup> At the clinic level, therefore, patients could be given negative antibody results, yet still be very infectious "super-shedders". The same group, using new assays to improve HIV detection in semen,<sup>73</sup> developed this concept considerably<sup>74,75</sup> to infer different infectivities at different stages of HIV-infection. By measuring HIV concentration in blood and semen samples from patients with acute and long-term infection, they observed that semen concentrations increase and decrease in approximate parallel with changes occurring in blood. Their models suggest that



**Fig. 7.7:** Probability of HIV transmission per coital act in monogamous, heterosexual, HIV-discordant couples in Rakai, Uganda<sup>70</sup> (reproduced with permission).



**Fig. 7.8:** The effects of intermittent STI on the probability of sexual transmission of HIV<sup>76</sup> (reproduced with permission).

acute dynamics alone are sufficient to increase probability of HIV-transmission by 8–20 times between peak levels, termed “ramped-up viremia” (day 20 after infection), and the virological “set-point” (day 54 and after).<sup>76</sup> During a long asymptomatic phase, the viral load would remain low, except during episodes of classic STI when there would be “break-through” increases in viral load in semen (Fig. 7.8). It should be emphasized that suppression of HIV in the genital tract by ARV is incomplete. Sadiq and colleagues reported detection of HIV in semen of subjects suppressed by ARV when they acquired STI; the variants they recovered were resistant to the ARV administered.<sup>77</sup> Given that many people with HIV acquire STI, such “break-through” viral loads could represent a significant risk for HIV transmission. In the last stages of HIV disease, when AIDS develops, the viral load would rise again, together with infectiousness, if the individual was still sexually active. To a considerable extent, this model of infectivity has dominated concepts of HIV infectiousness by stage of HIV infection, and the influence of other STI.

The same group also showed (using a pooling serum strategy to minimize costs) that antibody-negative sera could be screened for viral RNA. For example, 100,000 serum samples for blood donation were examined in “real time” over 12 months in North Carolina.<sup>78</sup> Twenty three positive subjects were identified; most, unsurprisingly, were found in STI clinics.

In a further analysis of Rakai data,<sup>79</sup> investigators “constructed” couples from the entire study population based on the subject’s histories, archived serum samples from seroconverters, and viral genetics. This approach allowed them to detect the transmission of HIV within couples even when both partners were HIV seronegative at the beginning of the study, and thereby calculate infectivity by stage of infection. The average rate of HIV transmission was 0.0082/coital act within 2.5 months after seroconversion of the index partner, 0.0015 within 6–15 months, 0.0007 among HIV-prevalent index partners, and 0.0028, 6–25 months before the death of the index partner. In an accompanying commentary,<sup>80</sup> it was further calculated that nearly one-half of the HIV-transmission events observed could be ascribed to a

#### Box 7.4 Odds of Detecting HIV in the Genital Tract<sup>86</sup>

Urethritis	OR 3.1; 95% CI 1.1–8.6
Cervicitis	OR 2.7; 95% CI 1.4–5.2
Cervical discharge/pus	OR 1.8; 95% CI 1.2–2.7
Gonorrhea	OR 1.8; 95% CI 1.2–2.7
Chlamydial infection	OR 1.8; 95% CI 1.1–3.1
Vulvovaginal candidiasis	OR 1.8; 95% CI 1.3–2.4

sex-partner with newly acquired HIV-infection; however, others have disputed this interpretation on the basis of unknown sexual behaviors, and generalizability to other populations with higher STI rates, and contracting HIV epidemics.<sup>81</sup> Similar objections have been raised by mathematical modelers.<sup>82,83</sup>

Nevertheless, in a study utilizing phylogenetic data (namely the generation of large volumes of sequences from the *pol* gene), epidemiological and cohort approaches were enhanced, and investigators from Vancouver showed that early infection accounted for approximately half of onward transmissions.<sup>84,85</sup>

With this extensive background of empiric and theoretical work on HIV-transmission, mostly based on measurements in blood, Johnson and Lewis conducted a comprehensive systematic review and meta-analysis of available data of the effects of genital tract infections on HIV-shedding in the genital tract.<sup>86</sup> Thirty-nine studies were examined. The odds of detecting HIV in the genital tract were increased in certain conditions (see Box 7.4).

Other infections and clinical conditions were found to have no significant effect on the detection of HIV, although HSV-2 shedding was found to increase the concentration of HIV, and GUD was found to increase the odds of HIV detection significantly, after exclusion of one biased study (OR 2.4, 95% CI 1.2–4.9).

The analysis showed that infections that are associated with significant increases in leukocyte concentrations in the genital tract are also associated with significant increases in HIV-shedding.

## Male Circumcision

The epidemiology of male circumcision is covered elsewhere in greater detail in Chapter 12, “Prevention of HIV and other sexually Transmitted Infections: Male Circumcision”.

Briefly, three RCTs showed a strong protective effect on HIV acquisition of about 60%. There were modest decreases in the incidence of HSV-2, *Trichomonas vaginalis*, papillomaviruses, and a small effect on syphilis. There were some indications of a greater efficacy of circumcision among men at higher risk in the Uganda trial (those with nonmarital partners, reporting transactional sex, or having a history of genital ulcers), namely, about 75% effect. This may be due in part to protecting against other STI, thus providing additional indirect protection against HIV. Overall, however, models estimate about 10–20% of the HIV infections prevented by male circumcision were due to efficacy against STI.

## Special Role of Genital Herpes (Especially HSV-2)

Studies of the role of HSV in HIV transmission were initially hampered by the low sensitivity of methods to detect HSV prior to the 1990s including virus isolation in tissue culture, cytologic examination, immunostaining, and antigen detection. The gold standard was viral culture, but the sensitivity dropped from nearly 100% in vesicular lesions to 30% in healing lesions.<sup>87</sup>

This all changed when PCR was developed for HSV,<sup>88,89</sup> and further refined for easy use in clinical settings.<sup>90,91</sup> Later, tests were developed to quantify the amount of herpes DNA.<sup>92</sup>

The new laboratory tools revolutionized investigations into the natural history of HSV-2, its world-wide distribution, and interactions with HIV.

In 2002, investigators used stored sera from the Mwanza trial<sup>93</sup> to show that HIV seroconversion was strongly associated with HSV-2 incidence; moreover, the next year Reynolds and colleagues in India demonstrated that hazard ratios for HIV incidence increased - the more recent the date of incident HSV-2 infection.<sup>94</sup> A substantial number of epidemiologic studies accumulated showing that prevalent HSV-2 was associated with a 2- to 4-fold increased risk of HIV acquisition.<sup>95</sup> In addition, most HIV-infected persons were also infected with HSV-2, and most experienced frequent subclinical and clinical reactivations, which elevated serum HIV-RNA levels. A systematic review and meta-analysis<sup>96</sup> showed HSV-2 positivity to be a significant risk factor for HIV acquisition in general populations of men (summary adjusted RR 2.7), women (RR3.1), and MSM (1.7).

The improved diagnosis of HSV-2 infection and improved control of STIs (especially chancroid and syphilis) clearly indicated that HSV-2 might be as important, or more important, than bacterial STI in promulgating the HIV epidemic,<sup>97</sup> and pointed the way toward the next step-evaluation of antiviral treatment of HSV-2 as a prevention strategy to reduce acquisition and transmission of HIV.

At the same time the biology and natural history of HSV-2 were becoming better understood, in particular, the frequency of subclinical reactivations, and the amount of HSV-2 and HIV shedding during these reactivations in coinfecting individuals.<sup>98–100</sup>

The next step evaluated, in three proof-of-concept RCTs, the effect of HSV-2 suppressive therapy with either 800 mg acyclovir daily or 1000 mg valacyclovir daily on HIV-1 genital or rectal shedding and plasma HIV-1 RNA. In these trials the strength and consistency of the observed reduction in HIV-1 replication and the biological plausibility of interactions between the viruses strongly suggested a causal relation between the replication of the two viruses<sup>101–103</sup> (Fig. 7.9).

Following these trials, Van de Perre and colleagues, in a comprehensive review,<sup>104</sup> explored the mechanisms that may operate to enhance reciprocal viral replication. Direct interactions could involve HIV-1 related immune deficiency, disruption of mucosal barrier by HSV infection/reactivation, HSV-induced

	HIV acquisition	HIV transmission
Strength of the association	✓	✓
Consistency of the association	✓	Limited data
Temporal relationship of association	✓	✓
Specificity of association		GUD (80% HSV-2 seroprevalence)
Biological plausibility	✓	✓

**Fig. 7.9:** Does HSV-2 facilitate HIV acquisition? HIV transmission? Celum C, ISSTD 2005 (reproduced with permission).

mucosal cell recruitment, transactivation of HIV-1 replication by HSV proteins, and immune modulation by HSV decoys. Indirect interactions might coexist through disturbances of the vaginal flora during HSV shedding and systemic immune activation. In coinfecting individuals, suppressive treatment reduces HIV-1 genital and systemic excretion. This finding is a likely result of efficacious prevention of HSV-2 reactivations, and perhaps of other herpes viruses.

Two very large RCTs were then conducted to assess the effect of acyclovir 400 mg twice daily on HIV incidence (the “acquisition link”) in 821 high-risk women in north-western Tanzania,<sup>105</sup> and women in various populations of Johannesburg (South Africa), Harare (Zimbabwe), Lusaka (Zambia), and MSM in San Francisco, Seattle, New York (USA), and Lima, Pucallpa, and Iquitos (Peru)—*n* = 3277 total.<sup>106</sup> No impact was observed in either trial, a profoundly disappointing result.

A randomized trial was next conducted to test “the transmission link”, by giving the same dose of acyclovir (400 mg twice daily) to serodiscordant couples for HIV (Partners in Prevention Trial). 3,408 couples were recruited at 14 sites in Africa. Despite a reduction in plasma HIV-RNA of 0.25log<sub>10</sub> copies per milliliter and a 75% reduction in GUD, there was no effect on the transmission of HIV-1, another profoundly disappointing result.<sup>107</sup>

It is possible that the dose of acyclovir used in these studies was not sufficient to reduce the HIV viral load (via reduction of HSV-2 reactivations) but enough to prevent HIV transmission, while still having sufficient effect to slow HIV disease progression. There is some evidence for both these hypotheses. First, higher doses of acyclovir (800 mg as a single dose), or valacyclovir (which has twice the half-life of acyclovir) have been associated with greater reductions in genital shedding of HIV-RNA<sup>101,103,108,109</sup> and second, acyclovir was shown to have a modest effect on HIV progression in a subsequent analysis of the Partners for Prevention trial<sup>110</sup>; the latter was not altogether surprising, a similar effect had been shown in the late 1990s,<sup>111,112</sup> presumably overshadowed at the time by the development of more powerful antivirals, directed specifically at HIV. Acyclovir has no direct effect on HIV replication, but in the meantime had been shown



to lower plasma HIV-1 RNA at any given CD4 cell count, when given daily for suppression of HSV-2 reactivations.<sup>113</sup>

Despite the disappointing results in the “acquisition” and “transmission” trials, to date there is no reason to doubt the enormous impact of HSV-2 on the HIV epidemic. HSV-2 is the leading cause of GUD worldwide. In Africa, HSV-2 seroprevalence in the general population ranges from 24% in West Africa to 74% in South Africa, mirroring the gradient of HIV infection rates.<sup>114</sup> Using seroprevalence data in mathematical models generated an estimate of 536 million infections worldwide, with 23 million new infections each year.<sup>115</sup> A study in Malawi<sup>116</sup> has shown that HSV-2 was already widespread in that country before the HIV epidemic and has not greatly been influenced by it. Sophisticated mathematical modeling<sup>117</sup> suggests that the role of HSV-2 as a biological cofactor in HIV acquisition and transmission may have contributed substantially to HIV, particularly by facilitating spread among the low-risk population with stable long-term sexual partnerships. In another modeling exercise, based on data from the Four Cities study,<sup>41</sup> it was also strongly suggested that HSV-2 therapy could potentially have a population-level impact on the incidence of HIV, especially in more concentrated epidemics. However, a substantial impact would require high coverage and long duration therapy, or very high symptom recognition and treatment-seeking behavior.<sup>118</sup>

In fact, the WHO published STI treatment guidelines in 2003,<sup>119</sup> which recommended that acyclovir should be included as a first-line GUD therapy in all countries where the relative prevalence of HSV-2 as an etiologic agent was 30% or higher. In 2009, an RCT in South Africa showed the benefits of early episodic acyclovir therapy (400 mg 3 times daily for 5 days), in terms of both ulcer healing, and reduction in HIV-lesional shedding.<sup>120</sup> A recent editorial emphasizes the importance of early initiation of episodic treatment in countries in the midst of an HIV/AIDS epidemic, where the natural history of HSV-2 infection has been radically altered by frequent recurrences and extended episodes.<sup>121</sup>

## A Return to Studies in MSM

At the beginning of this chapter, we discussed some of the shortcomings of early studies in MSM that attempted to infer causality for STI in HIV acquisition (the “acquisition” link).

Studies of STI/HIV interactions in MSM have a number of methodological limitations, including the same prime confounders as those in heterosexual populations, namely sexual behaviors. It is possible that there is a much greater variety of homosexual behavior(s), many of which are changing since the advent of ARV,<sup>122–126</sup> or under the influence of drugs and alcohol<sup>127–132</sup>; in addition, the behaviors of MSM in other non-Westernized societies have been poorly studied.<sup>133</sup> One recent prospective study controlled for many aspects of sexual behavior, and found anal gonorrhea (adjusted hazard ratio = 7.12, 95% CI 2.05–24.79) and anal warts (adjusted hazard ratio = 3.63, 95% CI 1.62–8.14) to be independently associated with HIV-acquisition.<sup>134</sup>

With respect to syphilis, a retrospective study of case records in Amsterdam revealed that a third of 81 HIV-positive patients had asymptomatic syphilis, a much higher percentage than in HIV-negative patients.<sup>135</sup> This accords with results obtained in Australia, where the incidence of syphilis was 5–10 times higher in HIV-positive than HIV-negative MSM.<sup>136</sup>

There are a few studies of the association of STI with HIV transmission in MSM (“the transmission link”).

A small study (n=7) of asymptomatic urethritis showed it to be independently associated with seminal HIV RNA shedding (adjusted OR 80.2) and with blood plasma viral load (adjusted OR 19.3)<sup>137</sup>; a larger study (n=55) of HIV-positive MSM not on ARV demonstrated that semen plasma viral loads were approximately 5-fold higher in those with gonococcal or chlamydial urethritis, compared to controls (4.27 log copies/ml versus 3.55 log copies/ml, respectively),<sup>138</sup> and a third showed drug resistant virus in semen to be 20-fold higher during gonorrhea, than following antibiotic treatment.<sup>139</sup>

The effects of syphilis on HIV viral load are inconsistent,<sup>140,141</sup> and syphilis does not appear to affect HIV disease progression, at least as measured by hazard of AIDS or death (hazard ratio 0.99).<sup>142</sup>

The only published references on HIV viral load in rectal mucosal secretions are from Zuckerman’s group in Lima, Peru and Seattle, Washington. In 27/64 MSM on ARV, they found higher median levels in rectal mucosal secretions (4.96 log copies/ml) than blood plasma (4.24 log copies) or seminal plasma (3.55 log copies).<sup>143</sup>

They took part in the Partners for Prevention trial of HSV-2 suppression, and found that valacyclovir resulted in a 0.16 log decrease in rectal HIV-1, and a 0.33 log decrease in plasma HIV-1 viral load, compared with respective values in the placebo arm, though it is unclear whether further studies on HIV-transmission in this group have been undertaken.<sup>144</sup>

Finally, circumcision does not appear to have much effect on STI or HIV in homosexual men, a result that is not entirely surprising, as it would only be expected to have a marked effect in MSM, whose sexual repertoire was entirely insertive.<sup>145,146</sup>

## Further Considerations

No one seriously disputes that HIV and STI influence each other in important ways, certainly at the level of the individual, and probably also at population level.

However, after the failure of five out of six African RCTs of bacterial STI control to prevent HIV, and even worse, the failure of the HSV-2 suppression trials—thought by many including the present author to be the strongest cofactor—investigators have been at a loss to explain the negative results. One of the chief proponents of circumcision—itself probably a crude debulking of the best target for pathogens—has called for a reassessment of what he views as a flawed hypothesis, namely that STI control could ever reduce HIV incidence.<sup>147</sup> Others claim that interventions were implemented during the wrong phases of most HIV



epidemics,<sup>148</sup> or just simply had multiple defects in trial design and implementation.<sup>149–152</sup> Thus far, little attention has been paid to the present state of ignorance of HSV-2 biology, and the biology and immunology of the reproductive, genitourinary, and GI tracts (including the rectum).

Austin Bradford Hill's famous considerations (and his invention, RCT) are probably both overinterpreted by those who would use them as criteria, and underappreciated by those who dismiss them as flawed. In fact, the heuristic value that epidemiologists place on them converges to zero as the complexity of a causal system, and the uncertainty about the true causal system increase.<sup>153,154</sup>

Finally, it seems increasingly likely that the interactions between HIV and STI are multifactorial, and that not enough emphasis has been placed on the complex social construction of sexual behaviors, including the situations that place individuals "at risk of risks".<sup>155</sup>

### Summary

Where possible the chapter is written as a narrative, highlighting themes, advances in laboratory techniques, as they occurred, and the population experiments that followed. It starts with the first description of AIDS and continues to the present.

In the 1980s and early 1990s, observational and other studies suggested an association between the presence of STIs and human immunodeficiency virus (HIV) transmission, by increasing either the infectiousness of the index case, the susceptibility of the partner, or both ("Epidemiological synergy", Wasserheit, 1992). However, the hypothesis that control of STIs can prevent the spread of HIV in populations has been extensively tested in community RCTs and is not supported by evidence in 7 of 8 trials. The equivocal results highlight the difficulty in assessing the effects of a single intervention and multiple causation, as well as the possible differential effects of STIs in early, mature, and late phases of an HIV epidemic. HIV and HSV-2 are known to be involved in a particularly vicious circle, with HIV facilitating acquisition and reactivation of HSV, and HSV in turn enhancing HIV acquisition and replication. However, several very large trials of HSV suppression have failed to demonstrate an effect on HIV acquisition, a profoundly disappointing result that remains perplexing. It has become evident that HSV biology is not well-understood. In contrast, three very large trials of circumcision in Africa have shown a remarkable, strong, and consistent protective effect of 50–60% on HIV acquisition (and some STIs). Finally, it seems increasingly likely that the interactions between HIV and STI are multifactorial, and that not enough emphasis has been placed on the complex social construction of sexual behaviors, including the situations that place individuals "at risk of risks".

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# section

## **PREVENTION AND CONTROL OF SEXUALLY TRANSMITTED INFECTIONS AND HIV**

— *Christopher Fairley*

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# 8

## Prevention Strategies for the Control of Sexually Transmitted Infections

Johannes van Dam

### Introduction

Sexually transmitted infections (STIs), including HIV infection, continue to be a major public health problem in many countries in the world, despite the availability of effective interventions to prevent acquisition and transmission of STIs and of effective antibiotics to treat and cure bacterial infections. Approaches to prevention and control of STIs and HIV infection differ according to the epidemiological situation, the cultural environment, the availability of resources, and the priority allocated to this group of diseases by health planners and decision makers. This chapter presents a conceptual framework for STI/HIV prevention and control, followed by a discussion of strategies for the prevention of infection and for case management. The importance of both individual and population level intervention strategies will be discussed.

### Conceptual Framework

#### DETERMINANTS OF STI AND HIV TRANSMISSION

At the most basic level, the STI and HIV situation in a population is determined by: (i) the rate of exposure of susceptible individuals to infection; (ii) the likelihood that such exposure results in infection; and (iii) the length of time that a newly infected individual remains infectious and, thus, able to spread the infection. This has been described in the following mathematical model:  $R_0 = c \times \beta \times D$ .<sup>1</sup>  $R_0$  is the reproductive rate of an infection or the mean number of secondary cases that will arise from any infected individual.

For situations where  $R_0$  is greater than one, the infection will continue to spread and incidence increases. When  $R_0$  is smaller than one, the incidence is decreasing and the infection will disappear from a population. The objective of all STI and prevention strategies is to reduce  $R_0$  to less than one, by influencing  $c$ ,  $\beta$ , or  $D$ , or, more likely, a combination of these.  $D$  is the duration of infectiousness;  $c$  is the average rate of exposure of a susceptible individual to an infectious partner and is thus determined by the rate of partner change, as well as the likelihood

that such partners are infected.  $\beta$  is the average likelihood of infection, when exposed to an infectious person.

STIs are not uniformly distributed over a community since behavioral characteristics differ between individuals and between subgroups in a population. Sexual behaviors differ, as do the number of sex partners and the rate of partners change, which in turn represent different levels of risk of infection. Individuals with the highest rates of partner change contribute disproportionately to the spread of STIs and are often referred to as “core transmitters”.<sup>2,3</sup> To understand the STI situation in a population, one also needs to know more about the patterns of sex partner mixing and of sexual networks. Consecutive partnerships are clearly less risky for the transmission of most STIs than are concurrent partnerships, which have been shown in mathematical models and clinical practice to dramatically increase the incidence of HIV infection and other STIs.<sup>4,5</sup> If individuals with high rates of partner change have sex with others who themselves have many partners, the potential for initial rapid spread is very high. This is especially the case in “dense” sexual networks, where there are many different partnerships in a short period of time.<sup>6</sup> Where individuals have partners mostly within their own social and behavioral group (so-called “assortative mixing”), spread of infections tends to be limited to the group. If some of these individuals have partners outside their own social group (also called “dissortative mixing”), STIs have the potential to spread more widely through a population, although they are likely to spread more slowly.<sup>7,8</sup>

From a public health perspective, effective interventions that reach individuals with high rates of partner change, who are in dense sexual networks with assortative mixing are likely to have the highest impact. One of the challenges for STI and HIV prevention programs is to identify and reach such individuals.

With the advent of effective antimicrobial agents in the 1950s and 1960s, STI control efforts focused for the most part on the clinical care of symptomatic individuals while relatively little attention was paid to behavioral interventions. Prevention was usually restricted to limited education of patients by clinicians to prevent future infections and occasionally to ensure partner

notification and treatment. The emergence and recognition of a number of viral STIs, and especially HIV infection, have underscored the importance of prevention. STI and HIV prevention efforts initially focused heavily on the individual, promoting safer sexual behavior, that is, abstinence, delayed onset of sexual activity for youth, reduction of the number of sex partners, and use of a barrier method to prevent infection, such as the male or female condom. It is now widely accepted that the social, cultural, and economic determinants of behavior need to be taken into account and, where possible, addressed.<sup>9</sup> Gender roles and inequities, power relations in sexual relationships, economic dependence, work-related migration, illiteracy, lack of access to information, and poverty all contribute to risky sexual behaviors. Many women, for instance, are well aware that they are at risk of acquiring an STI or HIV infection from their husbands, but are not in a situation to safely and effectively negotiate condom use.<sup>10</sup> For interventions targeting individual behavior to be successful, it is important that these be combined with community or population level approaches. In the absence of an enabling and supportive environment, many individuals may be unable or unwilling to adopt safer behaviors.

## INTERVENTION STRATEGIES TO PREVENT AND CONTROL STIs AND HIV INFECTION

As mentioned earlier, STI and HIV prevention strategies seek to reduce the reproductive rate of an infection by shortening the duration of infectivity, by reducing exposure of susceptible individuals to infection, and by lowering the efficiency of

**Table 8.1:** Basic Strategies for Prevention and Control of STIs and Sexually Transmitted HIV Infection<sup>11</sup>

*Decrease duration of infectivity (prevent further transmission and complications)*

- Treatment (curative or suppressive)
- Early treatment (case finding)
- Vaccine (therapeutic)

*Decrease exposure of susceptible individuals to infection*

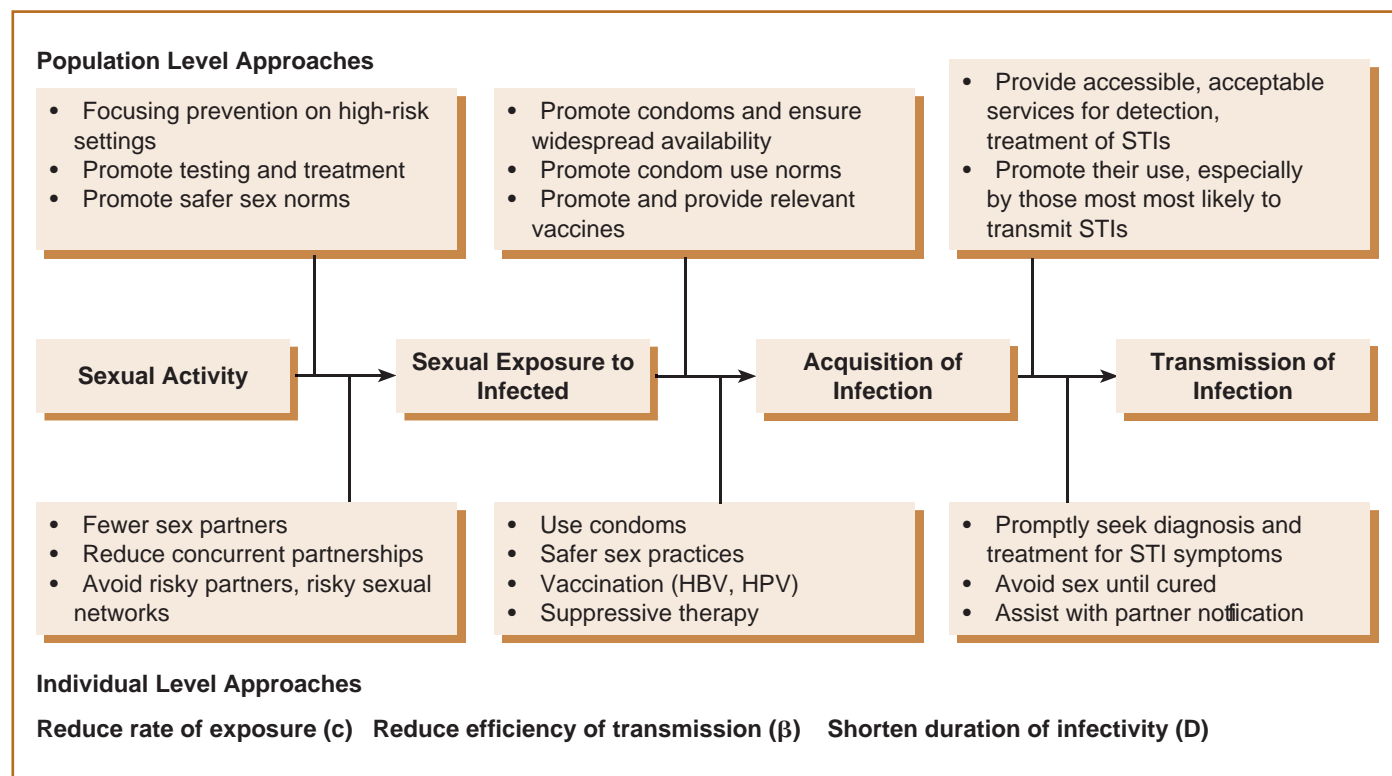
- Awareness/behavioral change interventions for susceptible individuals
- Behavioral change interventions for infected persons (especially for persistent viral infections)

*Decrease efficiency of transmission per exposure*

- Use of barrier methods
- Vaccine (protective)
- Use of microbicides

transmission for each such exposure. Basic strategies are summarized in Table 8.1.

The above strategies are both biomedical and behavioral in nature. While a vaccine offering protection against HIV has been elusive, a protective vaccine against Hepatitis B Virus (HBV) has been available for many years and in 2006 a vaccine against the most common carcinogenic strains of human papillomavirus (HPV) was approved for use in the UK, the USA, and in other countries.<sup>12</sup> In addition, for control programs to be successful, a combination of both individual and population level approaches is crucial. This conceptual framework is presented in Figure 8.1, which illustrates how both



**Fig. 8.1:** Individual and population-level approaches to STI and HIV prevention.<sup>13</sup>

individual and population level approaches act synergistically to prevent and control STIs, including HIV infection. It is important to note that for communicable diseases, individual interventions may well have an effect at the level of the population. For instance, effective treatment of infected individuals will result in a reduction of the prevalence of infection, and thus in reduced exposure of susceptible individuals to infected individuals.

For maximum impact, STI and HIV control programs require the implementation of a number of different interventions, as illustrated above. Few countries have been able to do so successfully, and it has proved difficult to overcome the social, cultural, religious, and above all resource constraints that prevail in many countries in the industrialized and the developing world. The Piot-Fransen model has frequently been used, in various adaptations, to demonstrate the results of insufficient, inadequate, or inappropriate program implementation. Figure 8.2 shows the cumulative effect of asymptomatic infections, poor symptom recognition, inappropriate healthcare seeking behavior, and inadequate clinical care, and demonstrates how, in many countries, only a small fraction of individuals infected with an STI in a population receives effective treatment. For instance, a study in South Africa showed that 25% of women surveyed were infected with at least one of the following infections: *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, or *Treponema pallidum*. Of these women, 48% were asymptomatic, 50% were symptomatic but not seeking care, 1.7% were symptomatic and would seek care, while only 0.3%

were actually seeking care the day they were surveyed.<sup>14</sup> Findings like this underscore the importance of a holistic, comprehensive approach to STI and HIV prevention and control. For instance, improving case management of symptomatic patients seeking medical care will neither address the problems of large numbers of asymptomatically infected persons, nor that of inappropriate healthcare seeking behavior or lack of access to good quality healthcare services.

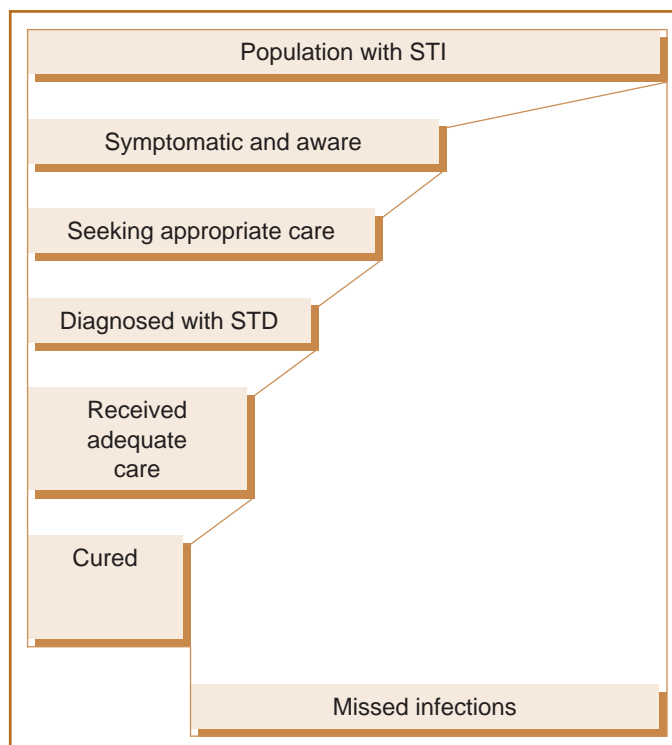
## Preventing New Infections

New infections can be prevented by reducing the prevalence of infections in the community, the use of preventive vaccines, such as those for HBV and HPV infection, and/or a reduction in or avoiding risk behavior at the individual level. Good quality effective clinical services are needed to reduce the prevalence of curable STIs, through the management and treatment of symptomatic and asymptomatic individuals with STIs. However, many STIs are of viral origin and thus currently not curable, and besides, clinical services are unlikely to identify and treat all individuals with curable infection. Thus, behavioral interventions remain crucial for the control of STIs and HIV infection.

The objective of such interventions is to reduce as much as possible the risk of infection through the adoption and maintenance of safer sexual behaviors. Examples of such behaviors are: abstinence, delay of sexual debut, nonpenetrative forms of sexual intercourse, reduction of the number of one's sex partners, and the use of barrier methods, such as the male and female condom or, possibly, microbicides.

For any of these behaviors to be adopted and maintained, individuals need not only to be aware of the existence of STIs, including HIV infection; they also need to recognize their own risk of infection. They need to know about safer alternatives and they need to have the means to implement these safer behaviors. In addition, the environment needs to be conducive to such behaviors.<sup>16–17</sup> Individual behavior is to a large extent influenced by the social and cultural context, that is, by partners, the extended family, peers, the community and, broadly speaking, existing norms. For maximum effectiveness, prevention programs should intervene at these different levels, and promote norms and behaviors that reduce the risk of acquisition and transmission of STIs. For instance, structural and policy interventions should support and mutually reinforce outreach by hospitals, community mobilization, and inter-personal interventions, such as peer outreach, couple counselling, or individual counseling.<sup>18</sup> Such interventions should promote delayed sexual initiation for those who are not yet sexually active; monogamy for those who are sexually active; avoiding concurrent sexual partnerships; and normalize the use of condoms.

An example of a multilevel intervention is the national HIV/AIDS prevention and control program in Thailand, which consists of, among others, a 100% condom use policy in brothels, a public education campaign, effective and easily available STI services, and outreach to sex workers and clients. It is credited with a substantial reduction in both STI and HIV infection rates in the Thai military.<sup>19,20</sup>



**Fig. 8.2:** The effect of poor healthcare seeking behavior and ineffective STD services on STI prevalence.<sup>15</sup>

The most effective approaches to prevention campaigns employ, thus, a combination of multilevel interventions, where the different interventions address the different influences on the individual. While mass media can be used effectively to raise awareness at the level of the population or a subgroup and may even influence cultural norms, these are likely to be much less effective in creating a good understanding of personal risk and vulnerability or in exploring options to reduce such risk.<sup>21</sup> When addressing the needs of marginalized or other hard-to-reach populations, interpersonal communication approaches are of the utmost importance. A successful communication program needs to identify and research its target audience, develop and pre-test messages specific to the objectives of the program and to the intended audience, and identify appropriate channels of communication.

### Improving Healthcare Seeking Behavior

An important element of an STI communication program is to raise awareness of the symptoms of STIs and the importance of early and appropriate treatment. Barriers to seeking appropriate and early treatment exist in many countries. The most common of these are ignorance of signs and symptoms of STIs, the stigma associated with STIs, and the lack of accessible and acceptable clinical services. The latter is often related to the poor quality of care offered through many such services and the frequently pejorative attitudes of healthcare workers to people with STIs.

Prior to initiating efforts to improve healthcare seeking behavior, it is important to do diagnostic research to identify the barriers to appropriate healthcare seeking behavior. For instance, integrating STI care with other, readily available services might reduce the degree to which stigma prevents people from seeking treatment. But improving the quality of care offered through public and private facilities, ensuring the availability of effective antibiotic treatment, and addressing the attitudes of healthcare workers may be necessary prerequisites to ensure the success of a communication program seeking to improve healthcare seeking behavior.

### Private Sector Involvement

In many countries, both in the industrialized and the developing world, the private sector is an important source of delivery of health services, and many STI patients prefer private sector providers as being more accessible, rapid, efficient, and anonymous.<sup>22</sup> There is now a slowly growing body of experience of interventions that seek to increase the role of the private sector in STI care and treatment. This experience ranges from voucher schemes to address issue of affordability, franchised services to increase access and quality, and interventions that seek to improve services offered by large employers to their workforce, such as the gold mining industry. Voucher schemes tend to be expensive to administer, although they might be cost-effective when used with high-risk populations.<sup>23</sup> Franchised services, where providers operate under a branded name and are

supported by advertising, training, supervision, and supplies, have been found to increase client satisfaction and to result in some improved health outcomes, although quality assurance remained an issue.<sup>24</sup> More research is needed to identify and evaluate approaches to more effectively utilize the private sector in the provision of quality STI services.

### Clinical Management of STIs

One of the cornerstones of STI control is the effective management of STIs. Early diagnosis and treatment prevent further transmission and the development of complications and late sequelae, and it has the potential to greatly reduce HIV transmission. Ideally, such case management is based on an etiological diagnosis and the provision of effective antimicrobial agents, combined with one-on-one health education and counseling for treatment adherence, abstinence during treatment, partner notification, and behavioral change, including condom promotion. Very few places in the world have the resources to provide such comprehensive case management for all or even the majority of people with symptomatic STIs. In most resource-constrained settings, there is little or no access to laboratory facilities needed for an etiological diagnosis of STIs, well-trained staff is in short supply while the workload is high, resulting in very short patient-provider interactions. Management of STI patients is thus often based on a clinical approach, that is: history and physical examination, supported by simple laboratory tests, if available.<sup>25</sup>

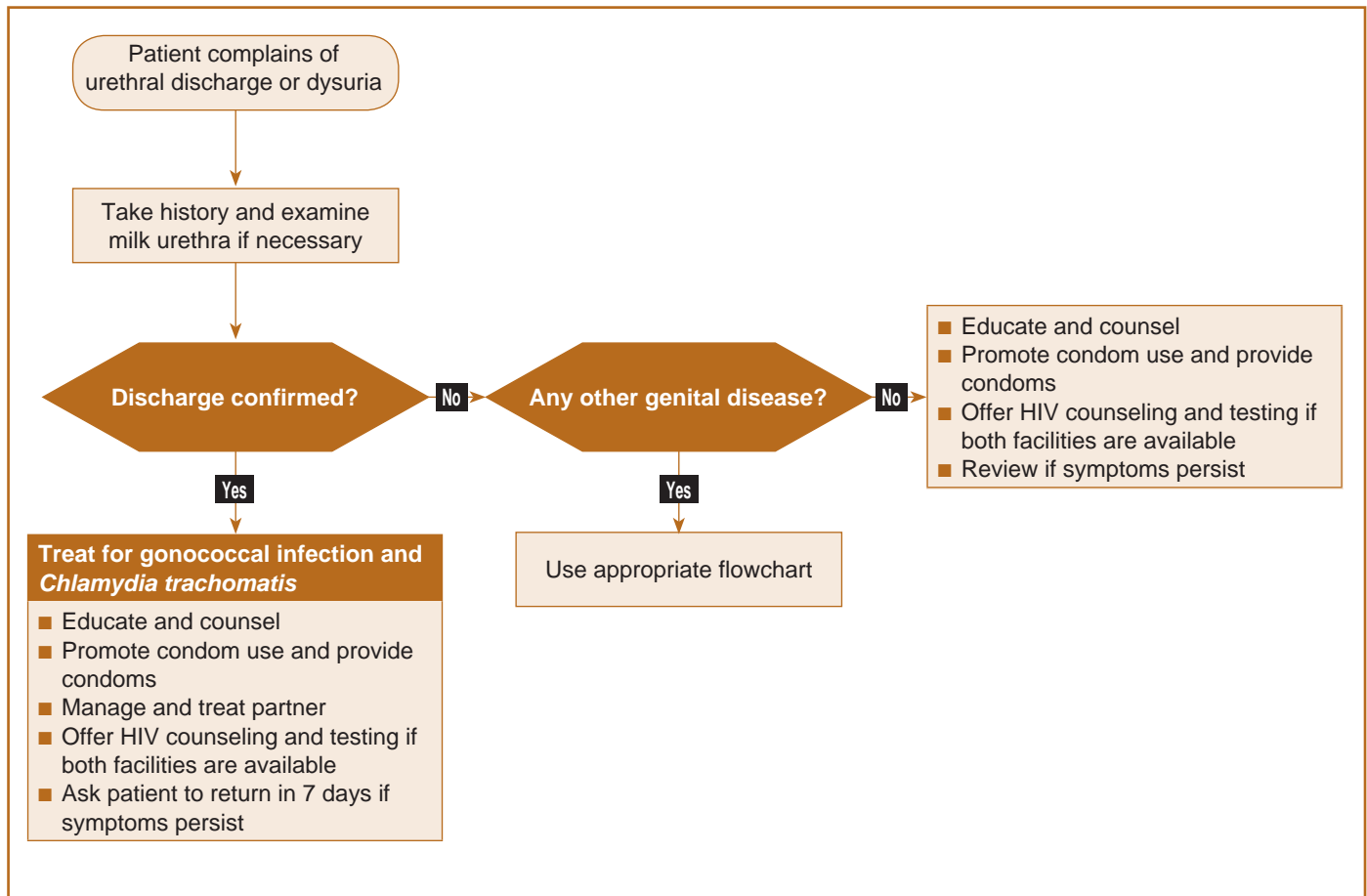
Syndromic approaches to STI case management have been developed and evaluated during the last 20 years. The syndromic approach is based on the following:

- (1) The recognition of relatively consistent and characteristic combinations of signs and symptoms (syndromes) with which STIs commonly present.
- (2) Knowledge of the most common local etiologies of the different syndromes.
- (3) Knowledge of the antimicrobial susceptibility patterns of these organisms.
- (4) Knowledge of the behavior and demographic characteristics of people with STIs.

Cure of patients with bacterial STIs is achieved through recognition of the presenting syndrome and provision of effective antibiotics against the most important causative organisms.<sup>26</sup> Promoting compliance with the treatment, counseling for risk reduction, condom promotion, and contact notification and treatment (the four “C’s”) are essential components of comprehensive care. Figure 8.3 provides an example of an algorithm to address the syndrome of urethral discharge, in a situation where microscopy is not available.

Where possible, laboratory tests can be added to increase the specificity of the algorithm. For instance, adding a microscopic examination of the gram-stained smear of the urethral exudates might reveal the presence or absence of gram-negative intracellular diplococci (ICDC). Where ICDC are present, treatment for both gonorrhea and chlamydial infection is indicated, while in the





**Fig. 8.3:** Algorithm for the management of urethral discharge. *Source:* WHO, Guidelines for the Management of Sexually Transmitted Infections, WHO 2003, Geneva, Switzerland.

absence of ICDC, treatment for gonorrhea can be omitted.

The syndromic approach has proven to be highly effective in the management of men with urethral discharge and of men and women with genital ulcer disease (GUD) of bacterial origin. Validation studies in Côte d'Ivoire and Kigali, Rwanda, for instance, showed cure rates of 100 and 99 percent, respectively, for genital ulcers using a syndromic approach.<sup>28,29</sup> Reports of increased prevalence of herpes simplex virus type 2 (HSV-2) among patients with GUD from, among others, Uganda and South Africa suggest that the currently recommended protocols for the syndromic management of GUD may be less effective in such situations.<sup>30,31</sup> In situations where HSV-2 is an important cause of genital ulceration, it may be indicated to add treatment for HSV-2 to the syndromic management of patients with GUD.<sup>32</sup> While the syndromic approach to the management of vaginal discharge is effective in addressing vaginitis, the most common cause of such discharge, it has proven to have low specificity and a low positive predictive value when used for the detection and management of cervical infections. Adding a locally appropriate risk assessment may improve the specificity somewhat, but the positive predictive value remains low in most situations.<sup>33,34</sup>

Rapid and simple laboratory tests that can detect gonococcal and chlamydial infection are urgently needed for the management of women, and also men, with asymptomatic gonococcal and chlamydial infections.

### Detection and Treatment of Asymptomatic Infections

A large proportion of women infected with a sexually transmitted organism are asymptomatic or only mildly symptomatic.<sup>11</sup> Large population-based studies have contributed to our understanding of the extent to which nonulcerative STIs in both men and women can be asymptomatic. For instance, 53% of men and 66% of women with gonorrhea, 92% of men and 76% of women with *Chlamydia*, and over 80% of women with trichomoniasis or bacterial vaginosis were asymptomatic in Rakai, Uganda.<sup>35</sup> Only 15% of men with either gonorrhea or chlamydial infection on a sample of rural men in Mwanza, Tanzania, were symptomatic.<sup>36</sup>

Where resources permit and diagnostic tests are available, case finding and screening can be implemented. Case finding and screening programs should initially focus on gonococcal

and chlamydial cervical infections, and on syphilis in men and women. The cost-effectiveness of such programs can be increased by identifying individuals at increased risk of infection through the application of a risk assessment, and to apply screening tests to individuals with a higher prior probability of being infected.<sup>26</sup> Screening of antenatal clinic (ANC) attenders for syphilis has been demonstrated to be a cost-effective public health intervention, even when the prevalence of syphilis among pregnant women is 1:20,000.<sup>37,38</sup> Even though screening of ANC attenders is a highly cost-effective public health intervention, programs are absent or inefficient in many countries. In Nairobi, Kenya, logistical and managerial constraints led to a situation where only 1 out of 11 women with reactive syphilis serology received treatment, whereas for 92% of ANC attenders blood was not taken, or, if it was taken, no results were available.<sup>39</sup> An important priority for any STI control program should be to implement a maternal syphilis screening and treatment program, or where such a screening program exists, to strengthen it to ensure complete coverage of all ANC attenders.

The syndromic approach by definition fails to identify asymptotically infected individuals. In situations where the prevalence of asymptomatic infections is high and where laboratory screening is not possible, mass or presumptive treatment has been successful in rapidly reducing the prevalence of STIs to very low levels.<sup>40</sup> Periodic presumptive STI treatment of sex workers in South Africa was successful not only in reducing rates of STIs in sex workers, but was also associated with a reduced incidence of STIs in male mine workers in the vicinity of the treatment site.<sup>41</sup> However, upon cessation of a mass treatment program, rates of infection tend to revert to preintervention levels in a relatively short period of time.<sup>42,43</sup> There is currently great interest in the application of so-called hybrid approaches, combining periodic presumptive treatment, especially of members of “core groups” with effective behavior change interventions, condom promotion, and good quality clinical services. Such a combination of interventions might allow for a much increased treatment interval in the periodic presumptive treatment program, while still keeping the prevalence of STIs low. Research is currently underway to examine the impact of such programs in Zimbabwe, Zambia, and South Africa.

An important group of potentially asymptomatic, but infected, individuals are the sex partners of a symptomatic patient. Ideally, the partners of an index patient are evaluated and the presence of an infection is established before treatment is initiated. Diagnostic tests, however, are not available for the majority of such contacts, and infection can thus rarely be confirmed. In such cases, epidemiological treatment of the partner or partners is indicated. This is treatment without a proper diagnosis, but based on the likelihood of a person being infected, and is recommended for the partner(s) of patients with gonorrhea, chlamydial infection, syphilis, and chancroid, and of patients with the syndrome of urethral discharge, GUD, or pelvic inflammatory disease.<sup>26</sup> Innovative approaches to partner treatment, such as expedited treatment where index patients are offered medication to give

to his or her partners have been associated with reduced rates of persistent or recurrent gonorrhea or chlamydial infection.<sup>44</sup> Great care should be taken to ensure that these approaches to the management of asymptotically infected individuals are gender sensitive and do not contribute to stigmatization of women.

## STI Treatment and HIV Prevention

A number of observational studies provide evidence that both ulcerative and nonulcerative STIs facilitate the transmission and acquisition of HIV infection.<sup>45</sup> Shedding of HIV in genital secretions is increased in the presence of STI-related inflammatory reactions and exudates from lesions, thus potentially rendering HIV-infected persons with concurrent STIs more infectious.<sup>46,47</sup> Cohen et al. demonstrated an eight-fold increase in viral load in seminal plasma in the presence of urethritis, and a subsequent reduction in viral load after treatment of the urethritis in Malawi.<sup>48</sup> In women with gonorrhea or chlamydial infection, there is an increase in the number of CD4+ lymphocytes (the target cell for HIV infection) in the endocervix.<sup>49</sup> Lastly, a community-based STD treatment trial in Mwanza, Tanzania, demonstrated a 42% reduction in HIV incidence in the intervention communities compared to the control communities.<sup>50</sup> This suggests that the benefits of effective STD treatment might be manifold; apart from the immediate benefit to the person infected, there might be a dynamic, population effect in reducing further transmission of the STIs as well as of HIV infection. Subsequent STI prevention and treatment trials did not result in a reduction in HIV incidence. The extent to which STD treatment might affect HIV transmission depends upon the background prevalence of HIV in the community, on the prevalence of high-risk sexual behavior, and on the types of STIs present in the community.<sup>51,52</sup>

## Clinical Management of HIV/AIDS

Treatment of AIDS with antiretroviral therapy is discussed in Chapter 68. Even with highly active antiretroviral therapy (HAART), it is currently not possible to eradicate HIV from the body, but it is nevertheless possible to reduce the viral load in the peripheral blood to very low or undetectable levels and HAART has been associated with a 50% reduction in morbidity and mortality.<sup>53,54</sup> In Rakai, Uganda, a direct relationship between plasma viral load and transmission of HIV was found, with the probability of transmission per sex act increasing from 0.0001 at viral loads of less than 1,700 copies/mL to 0.0023 per act when the viral load in the infected partner was 38,500 copies/mL or more.<sup>55</sup> While HAART also results in a reduction in the level of HIV-1 virions in seminal fluid, it has nevertheless been possible to detect replication-competent, and thus potentially infectious virus in the seminal fluid of men without detectable viral RNA in plasma.<sup>56</sup> It has been hypothesized that antiretroviral therapy might, in addition to conferring a benefit to the person taking the treatment, also contribute to reduced HIV transmission. Further study is needed to evaluate the impact on HIV transmission of antiretroviral therapy.

Recent findings from intervention trials have demonstrated the potential impact of antiretroviral based prevention approaches on HIV transmission. Studies among men who have sex with men,<sup>57</sup> heterosexual men and women,<sup>58</sup> and discordant couples<sup>59</sup> have all shown a protective effect of oral pre-exposure prophylaxis, ranging from 44% to 72%. Early treatment with ART of the infected partner in discordant couples reduced transmission by 96% in a large multi-country randomized controlled trial.<sup>60</sup>

## Conclusion

Successful prevention and control of STIs and HIV infection require the implementation of a combination of approaches, tailored to the epidemiological and resource situation in a country, while taking into account the cultural environment. Multilevel approaches are required for successful prevention programs, addressing both individual behavior as well as the sociocultural context within which individuals live and act. Early diagnosis and treatment of symptomatic STIs and, where possible, management of asymptomatic infections further contribute to prevention by reducing the transmissibility of HIV infection. Delivery of facility-based clinical services can be reinforced by periodic presumptive treatment of individuals at increased risk of infection, especially in situations where laboratory screening for case finding is not feasible. The syndromic approach to STD case management is still the most feasible option for the clinical management of the large majority of patients with symptomatic STIs, although rapid and simple diagnostic tests are essential for the effective management of gonococcal and chlamydial infections in women and to a lesser extent in men. A majority of patients with STIs seek care outside the public sector, and involvement of the private sector in improving the quality of STI service delivery is therefore crucial. Screening for the detection of syphilis in pregnant women is a highly cost-effective public health intervention and should be implemented or strengthened with the greatest urgency. Recent findings from HIV prevention trials have shown the potential for the use of ART-based prevention approaches to reduce both acquisition by HIV-uninfected individuals and transmission by HIV-infected individuals, through pre-exposure prophylaxis and early treatment, respectively. Lastly, prevention programs should be developed and implemented in a gender-sensitive way, appropriate to the needs of both men and women, while taking care not to stigmatize women.

### Summary

Successful prevention of sexually transmitted infections requires a combination of individual and population-level approaches that focus on reducing the risk of acquisition and transmission of infection. Both primary and secondary prevention are of crucial importance, and both the public and the private sectors have a role to play. Recent findings have underscored the importance of pre-exposure prophylaxis as well as early treatment in the primary prevention of HIV infection.

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# 9

## Behavioral and Counseling Aspects of Sexually Transmitted Infections (Including HIV)

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### Introduction

This chapter attempts to explain the beliefs underlying psychological reactions to sexually transmitted infections (STIs) and the reasons for psychological problems, as well as approaches to counseling them when they occur. There are a number of reasons why counseling is an integral part of treating patients with STIs including HIV. First, the management of the illness, and the prevention of further infection of others or reinfection, is based on a number of behaviors that may be positively influenced by counseling. These include cessation of unsafe sexual behavior and other actions likely to transmit pathogens, adherence to medication, and alteration of current and future sexual behavior to prevent reinfection after treatment. Second, STIs are different from most other conditions in being stigmatizing; indeed, even talking about sexual behavior, let alone about contracting an STI, causes difficulty for some health practitioners. In the case of widely publicized STIs, such as HIV infection and genital herpes, the stigmatization is sufficiently severe as to lead to overt discrimination. The degree of stigmatization may lead to psychological harm, including depression, anxiety or loss of self-esteem, as well as loss of social supports. While important in themselves, these factors in turn are likely to negatively influence risk behavior change, adherence with medication and other behavioral requirements for successful treatment, and avoidance of reinfection.

### Meaning of STIs to an Individual

Perhaps the earliest recorded account of an STI, probably syphilis, was in China in 6237 BC<sup>1</sup> yet little of a scientific nature has been written about the meaning of STI infection to the individual, and little empirical research has been carried out on this area.<sup>2</sup> In discussing the meaning of STIs to the individual, there appear to be at least five separate attributions in modern society.<sup>3</sup>

1. STIs are a deserved outcome of indiscriminate sexual behavior and punishment for sexual sins.
2. STIs are a consequence of individual inadequacy that leads to sexually indiscriminate behavior.

3. STIs are a consequence of a breakdown in traditional social values and rapid social change.
4. STIs are the result of an individual coming into intimate contact with a virulent pathogen.
5. STIs are a sign of being sexually active and a matter of pride.

There is a hierarchy of blame from attribution 1 to attribution 5. With the exception of attribution 5, the level of blame roughly parallels a similar hierarchy of the degree to which the individuals see themselves as responsible for the infection. However, it is important to recognize that different models will apply in different cultures and subcultures, and will depend on the degree to which there is a psychological investment in sexual behavior. Equally importantly, the meaning of STIs to the patient and to a lesser degree to the health practitioner will affect not only the adherence with treatment but also the psychological response to infection and probably the subsequent risks of exposure to STIs the patient takes. Diagnosing the psychological difficulties surrounding STIs will be made easier if the practitioner is able to assess the patient's understanding of what it means for her or him to have an STI. The practitioner can then in the counseling process intervene more effectively.<sup>3</sup>

### Counseling

#### CONCEPT OF COUNSELING

Counseling is sometimes a vague term which is loosely applied in health practice and is occasionally used synonymously with "talking". However, counseling is never *aimless* talking<sup>4</sup> but is a process of helping a person taking charge of his/her own life by developing the ability to make wise and realistic decisions, altering his/her own behavior to produce desirable consequences, and providing information. Counseling is an issue-centered and goal-oriented interaction and a confidential dialogue between a person and a care provider, in which the counselor offers his/her time, attention, and respect. Good counseling, including providing information that is tailored to the individual patient's need, helps the patient to be autonomous, i.e. to be able to choose, make decisions, and be responsible for his/her own actions.

## LEVELS OF COMMUNICATION IN COUNSELING

Counseling encompasses three levels of communication: permission, limited information, and specific suggestions. These levels correspond to three of the four levels of the PLISSIT model.<sup>5</sup> Originally, it was developed as a model of intervention of sexual health counseling. ‘P’ stands for a permissive atmosphere in which the patient feels free to talk about his/her concerns, including sexual issues. ‘LI’ stands for limited information. Giving information often goes hand in hand with giving permission. Frequently, this information serves to dispel myths or misconceptions. The information should be limited to specific facts directly relevant to the patient’s particular concerns. ‘SS’ refers to specific suggestions. Within the STI counseling setting, this level refers to STI-related risk reduction plans. ‘IT’ stands for intensive therapy. This level is not included in STI counseling, since the provision of intensive therapy is not part of the role of a STI counselor. These levels of communication require STI and HIV-related knowledge, self-awareness, and counseling skills and techniques on the part of the counselor.

### Self-Awareness

Self-awareness helps the counselor to: be aware of his/her own attitudes and values that (s)he brings to STI counseling; feel comfortable when discussing sensitive issues such as sexualities; separate his/her own feelings from those of the patient; and create a permissive attitude during the counseling session.

From the social environment where we grow, we develop certain stereotypes and prejudices about other people and other groups that have a major impact on our social and interpersonal interactions with other. These stereotypes and prejudices are reflected in our attitudes composing of 3 components: our thoughts, beliefs, and ideas (the cognitive component) quite often evoke feelings. Feelings (the emotional component) associated with attitudes can even turn into behavioral acts (the behavioral component) such as bashing commercial sex workers, men who have sex with men (MSM), certain ethnic groups, etc. Closely related to attitudes are values. They refer to beliefs that help the individual determine what is right and wrong, good or bad, and what is to be cherished. Attitudes and values exist within cultural and time contexts. Just as patients bring their attitudes and values to the counseling session, so do counselors. For example, within the STI context, the range of meanings of STIs described above are just as applicable for counselors. On the one hand, the counselor whose attribution of STIs is as a punishment will discourage avoidance of risks because the “punishment” is preordained and presumably unavoidable. Nor will any distinction be made between safer and unsafe sexual acts because the “punishment” is seen as being of for sexual activity, not specific sexual acts! On the other hand, the counselor who believes that sexuality is important and that STIs are just another infection may have less motivation to encourage individuals to modify their behaviors. Either extreme is unhelpful. Where counselors see sexual contact in moral or ideological terms –

the counselors need to address their own values and attitudes. Otherwise, the interaction between patients and counselors who hold conflicting attributions of HIV or STIs may also lead to tension, anger, transference and counter-transference issues, and to resistance to taking advice or to treatment, particularly where more divergent attributions are held. Our attitudes and values can also be challenged by the patient’s mode of functioning and attitudinal and value systems may clash when patient and counselor have different cultural/ethnic backgrounds. In other words, what is important to keep in mind is that our attitudes and values as counselors will affect our approach to our patients, and that our personal attitudes will interact with those of our patients. To be effective STI counselors, there is a need to be as aware as possible of one’s attitudes and values, in particular in relation to vulnerable groups, sexualities, and STIs.

It is crucial to remember that counselors have a right to their personal attitudes, morality, and values. But they should not impose their attitudes and values upon the patients. Counseling sessions may evoke feelings not only within the patient but also within the counselor. While the counselor cannot be held responsible for his/her feelings, (s)he has the responsibility for what (s)he does with his/her feelings.

### Counseling Skills and Techniques

Establishing and maintaining a professional relationship is crucial in all counseling. Unlike casual conversation, information that is exchanged and obtained in counseling is specific, focused, and serves a purpose. The STI counselor enters the private world of a patient and may have to facilitate the patient in being very explicit in describing sexual patterns of behaviors. Basic counseling skills are essential to conduct a dialogue with the patient. They can enable the patient to explore his/her problem, reach a better understanding of the problem, deal with her/his related feelings and concerns, evaluate alternatives, make choices and take action. Examples of counseling skills are empathy, attention, and listening.

The ability to be empathic is one of the crucial skills in counseling. Empathy is defined as including: (i) the affective capacity to share another’s feelings, and (ii) the cognitive ability to understand another person’s feelings and perspective. Sometimes the definition also includes the ability to communicate one’s empathetic feelings and understanding to another person by verbal and/or nonverbal means. Carl Rogers<sup>6</sup> wrote “...the state of empathy or being empathic is to perceive the internal frame of reference of another with accuracy and with the emotional components and means which pertain thereto as if one were the person, but without ever losing the ‘as if’ condition.”

Attention and listening are closely related to one another. They refer to the behavioral skills that by focused listening pay close attention to the patient, limiting distractions, and equalizing the power between the counselor and the patient. As an attentive listener, the STI counselor should try to pick up the patient’s experiences, behavior, feelings, and point of view when talking about his/her experience, behavior, and feelings. The counselor

should also allow the patient to find out his or her own solution if (s)he can. If (s)he needs help, avoid ordering him/her to do things. Give suggestions from which he/she may be able to choose.

There are many different counseling techniques such as open questioning, paraphrasing, reflecting feelings, clarifying, repeating, probes, summarizing, and nondirective approach.

To summarize, an STI counselor is empathic, well-informed, not biased/judgmental/condemning, not emotionally involved (compassionate people should guard against this), authentic/genuine, open-minded; and warm, friendly, calm, patient, understanding, flexible, and creative. It is important to remember that STI knowledge, self-awareness, and developing counseling skills and techniques are an ongoing process and our competence as counselors can always improve and be refined.

## THE AIM OF STI/HIV COUNSELING

The overall aim of STI counseling is to prevent future occurrences of other STIs for the patient and transmission of the disease to others by initiating a reflective process of developing a realistic risk-reduction plan (if time so permits) or at least inform the patient about safer sex behavior. It is also to help him/her to have a realistic understanding of the STI, and to educate him/her about necessary treatment.

## COUNSELING PROCESS IN STI MANAGEMENT

Probably the most important starting point is for the counselor to give the patient an opportunity to express discomfort and for the counselor to recognize this discomfort. Most patients have usually thought quite a lot about the issues before they consult a counselor and often have arrived at some conclusions about the nature of their problems. STI/HIV counseling is a process divided into pre- and post-test counseling.

## Revealing Details of Sexuality

Sometimes, especially in more stigmatizing contexts or where such behavior may be illegal, patients may not reveal crucial details of their sexuality (e.g., that they have contact with people of the same sex, with commercial sex workers, as a result of incest or sexual assault, or with under-age partners). Such patients are likely to conceal aspects of their sexuality from most people, to expect the most negative social reaction to their sexuality from significant others, society in general, and their health practitioner in particular. Where the practitioner is required by law to report particular behaviors, such nonadmission may be understandable. This has a number of practical applications for counseling. As lack of previous STIs in nonadmitters suggests that the clinic situation will be a new and potentially frightening one, in which condemnation is expected; in subsequent visits to a clinic, the patient will tend to be less apprehensive if the clinician's approach has been nonjudgmental. Thus, the first part of the visit is crucial in building up the rapport that is so critical for taking sexual histories and for sexual counseling. The apparent passivity and

lack of assertion that are also predictors of failure to reveal matters about one's sexuality, suggest that many patients may have trouble expressing what is construed as negative information that may elicit a negative response. It may also be that when counselors take histories in a manner that implies any sexual contact was a heterosexual or homosexual one, or consensual, the patient may not have the courage to make a correction.

However, these psychological factors will clearly operate in interaction with environmental factors such as the clinic, the clinician, and the legal and social climate regarding sexuality. Individual practitioners can do little more than to be aware of the factors operating, and seek to actively mitigate them through their interaction with patients, particularly emphasizing genuineness and empathy as well as specifically dealing with their therapeutic acceptance or what patients may consider shameful or abnormal practices. The imposition of shame and guilt upon sexual interactions by religious and other traditional moralities is the single most important cause of psychological problems in STI treatment, and if the practitioner is able to assess and deal with this early in the treatment process, many difficulties may be prevented or minimized. Lack of consideration may even introduce or reinforce shame or guilt and produce an iatrogenically strengthened distress. A high index of suspicion for psychosocial problems attendant on STI infection or reported infection is mandatory to ensure accuracy in history taking and maximal adherence with treatment, contact tracing or partner notification, prevention and preventive education and the possible contribution of psychosocial factors to relapse or reinfection should not be underestimated. It can, however, be to some extent neutralized by careful, sympathetic, and tactful handling.

## Pre-Test Counseling

Pre-test counseling encompasses informative and preventive components. The informative component refers to addressing the test to be taken and the possible treatments of the condition and possibility of transmitting the condition to others. When the patient actively seeks HIV counseling and testing services (i.e., patient-initiated counseling and testing), the informative component addresses issues such as the desirability and implications of taking an HIV test, the clinical benefits of testing and the potential risks (discrimination, abandonment, etc), as well as its voluntary nature. In all STI counseling, an opportunity should always be provided for the patient to ask the counselor questions.

The preventive component of all STI counseling focuses on the patient's own unique circumstances and risk taking and should help the patient to reflect upon his/her risk behaviors and ways to reduce the risks. However, STI/HIV prevention education varies widely from highly effective interventions to useless imparting of information that leaves the patient confused and feeling trivialized. Just providing a pamphlet or launching into condom directions use is insufficient for most people to modify their behavior, although written materials should certainly



be provided as background and back-up information. Help the patient to identify risk factors and cofactors: When are you most at risk for engaging in unsafe sex? What things make it more likely for you not to use a condom? Focus on behavior patterns. While some patients may prefer to see an STI or HIV as a “freak” occurrence, for example the monogamous wife infected by her husband’s extramarital contacts, other STIs occur following a *pattern* of risk behavior. Work with the patient to develop an individualized plan to prevent further STIs if this latter scenario is the case. For example, if a patient is more likely to engage in unprotected sex when feeling depressed, ask the person to identify early signs of depression for her or him, and then work together on solving the problem. What specific situations for the future are of most concern? In developing an individual plan, keep in mind that small changes in behavior are more manageable and successful than total lifestyle changes.

Just telling a patient to use condoms is not sufficient. If patients report a dislike of using condoms, work with them to identify the reasons they don’t use them, then develop a realistic plan for introducing condom use into future sexual activity. For example, if a man complains that he has decreased sensitivity when using condoms, you can suggest putting some lubricant inside the tip, or partners using the “female” condom. A couple who don’t use condoms because they are married or “in love” can be encouraged to examine the idea that part of loving is looking after one’s own and one’s partner’s health. The man who fears erectile failure or inability to ejaculate when using condoms can be assisted by reframing the problem to focus specifically on these concerns. While most sexually active patients have experimented with condoms at least once, some patients may report never having used condoms. In these cases, demonstrating condom use in the counselor’s office is most effective. In particular, having the patient handle the condom and practice putting it on by demonstrating on two of their fingers increases the chance of future use. Consider referral for follow-up counseling as appropriate.

A helpful insight is to view risk behavior both as a problem in itself and as possibly symptomatic of other underlying concerns. Studies in HIV prevention have identified many cofactors of risk including concurrent drug/alcohol use, depression, and other mental health concerns; sexual anxiety; history of sexual abuse; lack of assertiveness; and in some contexts, sexual orientation.<sup>3</sup>

Counselors need to be flexible with regard to what extent the preventive component should be at focus when conducting pre-test counseling. It should also be noted that the patient is entitled to refuse receiving counseling in any form. If a disease is notifiable to a government department, especially by name or other identifying details, this should also be disclosed.

## Post-Test Counseling

During the post-test counseling session the patient is notified about his/her STI/HIV test result. The session includes care/support, informative, and preventive aspects.

## Care/Support Aspect

For patients being notified of an STI diagnosis, they should be provided comprehensive and thorough care encompassing medical treatment and if needed psychological care to reduce psychological sequelae of the STI diagnosis. Appropriate referral when needed should also be provided. It is not uncommon that patients being diagnosed with an STI may experience feelings of being “punished” for sexual activity, loss of self-esteem because of the contraction of an, from their point of view, unacceptable disease. It may also have effects on the primary relationship in making spouse or partner aware that their partner has had sexual contact outside their relationship. This latter result of an STI may itself include sequelae such as relationship breakdown, depression or anxiety, or severe or dysfunctional guilt.

Along with the potential psychological sequelae, it is important to note that any STI diagnosis may have sexual sequelae. For some recurrent STIs, such as genital herpes as well as HIV infection, there are also recurrent sexual problems that need to be dealt with.<sup>3,7</sup> While the sexual problems are less well-documented and defined, several patterns exist. For many, possibly most, patients they experience a loss of sexual desire and even sexual functioning in conjunction with the diagnosis. They describe their sexual desire as having left them and the length of the “lost sexuality” differs between patients. While many patients may not be sexual with others, they may begin through masturbation to adjust sexually. Some men and women describe relating to their semen and vaginal fluids in a new way, seeing them as dirty and dangerous, symbolic of the disease that infected them. Eventually the person’s sexuality and sexual behavior patterns start and may return to the levels existing prior to diagnosis, with the exception that safer sex for many people takes on a new importance. MSM diagnosed with HIV quite often select other HIV-positive persons (i.e. “serosorting”) as sex partner, often via the Internet or organizations for people living with HIV.

It is helpful for counselors to view sexual activity as part of a person’s wider perspectives on life and adaptations. Whether through masturbation, sex with a significant other, or casual sexual activity, most people find sex to be powerfully releasing, distracting, grounding, affirming, and/or reassuring. Focusing on sex as a “problem” is not only counter to most people’s experience of sex, but may limit the credibility of the counselor as a source of advice, casting them instead as a moral agent or authority. People undergoing profound stress, including the newly diagnosed, may also use sex to cope with the stress (both functionally and dysfunctionally). A small minority of newly diagnosed persons with HIV may binge sexually following diagnosis. While some authors have suggested that this is an angry retribution reaction, in our experience it occurs primarily in persons with a history of compulsive sexual behavior and may more accurately and simply be defined as a person having a “slip-up” into a previous behavioral pattern. When testing for HIV, asking patients how they have coped with previous stressors and taking a good sexual history will clearly be helpful, as these may predict and prevent such behavior.



### Informative Aspect

Given the meanings of STIs discussed above, it is important to understand what having an STI means to the patient. In counseling, the aim should be to assist the patient to gain a realistic understanding: not so pathologized that the patient suffers significant psychological harm, nor so trivialized that the patient dismisses the infection as unimportant. In most cases, the patient is likely to overpathologize; hence it is important to balance this tendency with reassuring information. In some cases, particularly where the person feared the symptoms were those of HIV, diagnosis with a (non-HIV) STI may actually be a relief to the patient. Therefore, it is important to ask the patient how he or she feels and what they are thinking following diagnosis. Providing written or easy-to-understand information on the particular STI is important. Normalizing feelings of guilt and shame as transient reactions following an STI can also be helpful. For STIs that are likely to be recurrent (e.g., herpes) or chronic (e.g., HIV disease), the counselor should spend time reviewing what signs and symptoms a patient should note, and that infectivity may occur without signs or symptoms. In particular, patients need specific direction on when they can resume sexual activity, and when condoms must be used.

Another informative aspect is related to STI treatment. Obviously, this will vary according to the specific STI(s) diagnosed. Particularly in cross-cultural settings and settings where language is a barrier, it is important to ensure instructions are clearly understood. When providing oral medication, for example, ensure that the patient knows to take the medication orally, not as a suppository. Ensure that medication is taken under appropriate conditions (liquid, food, timing), and particularly, that antibiotic courses are completed or antiretroviral treatment (ART) is taken regularly to keep the viral load undetectable and to prevent development of drug-resistant strains. Asking the patient to repeat back to you any medication instructions can clarify the patient's understanding.

### Preventive Aspect

This aspect refers to behavioral changes (individual level) and STI disclosure to sex partner (interpersonal level). It is important to address unsafe sex patterns, particularly with persons living with HIV. Rather than giving advice – “you must always practice safer sex” – it is more helpful for the health professional to establish a relationship where both practitioner and patient can raise safer-sex concerns. Rosser et al.<sup>8</sup> in a recent study of 106 HIV positive persons found that one in four HIV positive persons admitted having unprotected sex with HIV negative or HIV status unknown persons post-diagnosis, and 10% believed they had infected others post-diagnosis. HIV positive persons having unsafe sex did not differ from positives who maintained safer sex—both knew the rules and had experience with safer sex. Hence, providing safer-sex education is not sufficient; one must specifically address the unsafe sex. The goal of such counseling should be to promote the sexual well-being of the patient: first,

by assisting the patient to recognize his or her risk behavior patterns, antecedents, and cofactors; and second, by addressing these patterns through counseling, treatment, and referral. It is also important that counselors address the window period and risk reduction strategies with patients receiving an HIV negative test result.

The other component of the preventive aspect is disclosure to sex partner of one's STI to prevent patient reinfection and to prevent further spread of the particular disease. Patients can themselves tell current or future partners about their STI/HIV or inform their partner(s) through partner notification. However, partner notification is to many patients a sensitive area and needs careful explanation as patients are often initially reluctant to contact partners. Where both partners are being simultaneously treated by the practitioner, relationship counseling may often need to occur as a function of one patient blaming the other for the STI or because the exposure of outside sexual contact leads to strains in the relationship.

Many patients perceive STI disclosure as stressful, which should not be underestimated. Without summarizing in detail the many issues that STI may elicit or precipitate, it is important to note two points. First, the counselor might be the only individual with whom the patient will be able to discuss the infection (and thus fulfils an important role as a supportive listener for a wide range of conflicts and concerns). Second, as already noted, the stigmatization surrounding HIV and some other STIs may precipitate a number of dysphoric mood states, or identity or relationship crises, which require just as much in the way of identification and management as will the infection itself. Great care should be taken to avoid recommending disclosure that may exacerbate the patient's situation and lead to serious discrimination or threats to life or livelihood. Obviously, balancing disclosure and threat of discrimination must be tailored to each individual case and carefully weighed. Such decisions need to be made by the fully informed patient, not the counselor!

### Staging of Reactions to HIV and AIDS

The emotional impact of HIV infection appears to be qualitatively and quantitatively different from that of curable STIs.<sup>9</sup> A diagnosis of herpes may be assumed to have a similar, if lesser, impact, given that the disease is incurable, if not life-threatening.

There are stages of response to the diagnosis through which individuals may pass. In many ways, these stages are similar to those described by Elizabeth Kübler-Ross<sup>10</sup> in her description of patterns seen when a person is coming to terms with a diagnosis of terminal illness. They do, however, differ in some important respects since the trauma may include stigmatization as well as the possibility of death. Ross et al.<sup>11</sup> have described the reactions of homosexual men to asymptomatic HIV infection. They note that HIV infection may not lead to death, and hence the Kübler-Ross<sup>10</sup> model of response to a terminal diagnosis may not always be appropriate. The stages bear some similarities to models of homosexual identity formation. This is to be expected. Firstly,

there is considerable stigma attached to infection with HIV or herpes and the stigmatized status is not usually visible or identifiable. Secondly, a significant proportion of individuals carrying antibodies to HIV in the western world are homosexual or bisexual men. In many cases they will use a previously appropriate and successful coping strategy to manage a second stigmatized status. The authors note that individuals may show retrogression as well as progression between stages: some individuals may neither experience every stage nor go beyond a certain point. It might also be of value for the practitioner to be aware that in close-knit relationships, the patient's partner may pass through these stages in parallel with him or her.

Shock, denial, and anger may be a first reaction to discovery that one is infected with HIV, and this may be exacerbated by stigma associated not only with HIV but also by stereotyping of individuals with HIV as acquiring the infection by being sexually immoral. Helpful responses by the health practitioner are to be quietly supportive and to allow the person to progress at his or her own rate. During the early phases, the person cannot take in much information; therefore it is appropriate to avoid overload. It may not always be helpful to encourage patients to express their emotions, especially in denial or where the emotions are unmanageable. Take your cues from the patient! At this point it can be a good thing to review with the patient a plan of action between this initial session and follow-up (ideally 48–72 hours following diagnosis).

The recognition that one has an HIV infection may lead to withdrawal. This recognition may lead to isolation, either imposed or self-imposed, sexual, or social. Recognition of the stigma associated with infection may activate previously successful coping strategies in groups such as homosexuals and injecting drug users. Individuals at this stage tend to keep to themselves as part of their uncertainty about the reactions of others. In an extended family situation, the reaction of other members of the family may be threatening or rejecting. Other salient factors in the withdrawal may be related to fear of infecting others and to depression. One of the reasons why a follow-up appointment after diagnosis is appropriate is that it allows you to monitor how withdrawn the patient has become. The roles of the practitioner during this phase include monitoring the patient's isolation (and in some circumstances, suicidal ideation) and being a confidante of the patient.

The individual who is positive for HIV antibodies or herpes infection typically discloses the situation to those who are most likely to be accepting, family, or significant others. Psychological processes may include negotiating the need for acceptance, expressing the need still to be loved and displacing stress onto people taken into confidence. The health practitioner's role during this phase includes being a resource for the patient, their family, and their significant others where appropriate. For the newly diagnosed person, the practitioner can assist by being a "safe person" for discussing how to disclose infectious status and to whom. Wherever possible, it is helpful for the practitioner to gently place the question of whom to tell back on the patient,

discussing the pros and cons of disclosure in each individual case. As the patient tells others, he or she may have specific questions about HIV, safety from infection and so forth. Others may need help processing their emotional reactions.

It may also be helpful for the patient to locate other people in a similar situation, looking for the social and psychological support of those with a similar diagnosis. Sharing problems and reactions with those "in the same boat" is a potent source of information, comfort, and coping strategies. Previously the practitioner's role may have been a rather dominant one, journeying with the patient during his or her adjustment. Now the role may be to refer on to support groups. Self-help groups may foster acceptance and provide the patient with skills and confidence to play a more active role in managing the disease. The practitioner's role now includes affirming the patient's developmental process in managing the disease. The desire to help others in a similar situation may be part of the process of "making friends with one's disease" and gives purpose in a life disrupted by the diagnosis and enhances coping. The primary role of the practitioner is to assist the person to make their decisions in freedom, to explore motivations, and as with all health concerns to assist the patient to make decisions that are healthy and realistic. In time, integration of positive HIV status as part of the patient's identity occurs.

These "stages" – while by no means invariable or a regular progression – illustrate that for the same diagnosis, different patients may not only be at different "stages" but may also progress (or regress) and be dealing with different psychological issues at different times. While no one strategy is appropriate for everyone, for healthy long-term adjustment a patient-empowerment approach is usually recommended. Such an approach views health practitioners as important consultants – part of a team coordinated by an informed patient who is the manager of his or her health. For health practitioners and patients who use such a style, the practitioner–patient relationship is often experienced as powerful, and as part of the best tradition of healthcare. Here, authoritarian, unilateral decision-making by practitioners is inappropriate and potentially harmful, especially where the patient is progressing through stages of coming to terms with the disease and the practitioner is not moving at the same pace. The patient's perceptions of cooperation and care are paramount in their interpretation, even if they do not coincide with the view of the practitioner: the patient will always see their own perspective as the "real" one.

### Sick Role Behaviors in STIs

In the case of individuals with an erroneous conviction that they have an STI, which Hart<sup>12</sup> refers to as venereoneurosis, the person displays both general hypochondriasis and a strong disease conviction without demonstrable evidence of infection. It most commonly occurs in patients who see STI as punishment for some real or imagined misdeed, usually of a sexual nature. The attention given to HIV infection has made "AIDS phobias" a clinical phenomenon. The individuals presenting with the phobia are usually concerned over sexual contact outside primary

relationships and are experiencing stress at work or in relationships, which often acts as a trigger. Ross<sup>3,13</sup> has suggested that when such patients are provided with insight into the additional factors that have led them to present with their concern at this time, the issue of HIV infection will often drop away and the other concerns (guilt over sexual behavior or outside sexual relationships for which the possibility of HIV infection is “punishment”) will emerge. There may also be an indication that the patient believes he or she “deserve” the infection. Brief insight-oriented counseling is the treatment of choice provided there is no evidence of psychosis. It is important not to perform repeated HIV testing, which may only reinforce the patient’s conviction of infection. Paradoxical interventions have been suggested as appropriate to psychotherapy for people with intractable HIV worry, but these interventions (which involve treating individuals as if they were infected in order to release them from their rigid and distressing beliefs) should be carried out only by competent psychotherapists.

Illness behavior refers to how a person responds to illness. In the case of most sickness, there may be a “sick role” associated with the condition and people may receive support and comfort from others (referred to as secondary gain). However, for stigmatized conditions, there may be no illness-related behavior because not only would there be no secondary gain, but secondary loss. It is thus not surprising that sick role behaviors in STIs do not occur as they do with most other medical conditions. The reaction of individuals – which is perhaps most commonly found – is a refusal to see STI as an illness; rather, it may be regarded only as a minor nonsignificant risk of a particular lifestyle. Clinical observation has tended to suggest that in the case of the absence of illness behavior, patients may frequently compromise treatment: by discontinuing medication after symptoms have resolved; by continuing sexual activity after symptom resolution but before clearance; or by not returning for proof of cure. Thus, both abnormal illness behavior such as disease phobias and lack of normal sick role or illness behavior may have implications for the management of STIs.<sup>14</sup> Compared with other illness behaviors, in which there may be substantial secondary gain from sympathy and assistance, STI infection appears to be quite different and to develop as a function of repeated infections. In such cases, would appear that STI infection tends to be seen as a chance event until several infections have occurred, when it is then seen not only as an illness<sup>12</sup> but also as a result of particular behaviors. It has been noted, using non-STI controls attending general practice and psychiatric outpatient clinics, that the STI clinic population is closer to the psychiatric population than the general practice one. This is consistent with the finding of Catalan et al.<sup>15</sup> that 40% of a United Kingdom STI clinic population had some degree of psychological disturbance on a screening test. It is unclear whether the disturbance was a function of having a stigmatized illness such as an STI or inherent in STI clinic attenders. There may be major differences between public and private clinics, and between the accuracy of histories at STI clinics, depending on individual factors such as practitioner approach and clinic environment.

## Conclusion

Psychological aspects of STIs play a central part in understanding the incidence, presentation, treatment, and prevention of these diseases. This is particularly true where the infection is not curable or is associated with stigmatization (e.g., HIV infection). In sexual counseling within the context of managing STIs, the psychological aspects of the problem may cause as much or more morbidity and distress as the physical ones, and these reactions need to be understood and treated by the counselor. Understanding some of the ramifications of STIs (including HIV infection) that are described in this chapter, as well as some of the counseling approaches to them, should place the counselor in a good position to deal with them in clinical practice. The goals of counseling should include accuracy in history taking and treatment, and promoting the sexual wellbeing of persons with STIs/HIV and the communities and networks within which they make their sexual contacts.

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# Role of Behavioral Interventions in Prevention and Control of Sexually Transmitted Infections and HIV

Devinder Mohan Thappa • Amiya Kumar Nath

# 10

Human behavior is the result of the complex interactions of physical and mental factors.<sup>1</sup> All forms of behavior are responses to stimuli like environmental stimuli, emotion and feelings, needs, motivation, and intellectual perceptions. Moreover, behavior is also described as an adjustment to meet the need of a given situation. Behaviors of an individual or communities are influenced by factors such as knowledge, beliefs, values, attitudes, skills, finance, materials, time, and also by the influence of other members of the society like family members, friends, coworkers, opinion leaders, and health workers. Pervasive issues like prevailing norms, male/female roles, ethnic discrimination, poverty, unemployment, and educational opportunities may limit the ability of a certain section of the society to behave in a healthy manner. Health behavior refers to those activities which people undertake to avoid disease and the efforts they make to facilitate the detection of asymptomatic infections through appropriate screening tests. Illness behavior refers to how people react to symptoms, and how quickly they seek help (medical or otherwise). Treatment behavior refers to those activities used to cure diseases like taking adequate medication, reporting for follow-up, etc.<sup>1</sup>

The means of sexual expression are infinitely greater than those that are acknowledged or sanctioned by the defined legal and moral systems of most societies which either openly or clandestinely provide opportunities for varied sexual expressions. Sexual behavior typically does not occur in public, making it difficult to motivate protection when potential transmission occurs.<sup>2</sup> Factors related to STI-associated risk behaviors are dependent on various aspects of individual characteristics like his/her social interactions and characteristics of the school, community, and society<sup>3</sup> with which they are associated.<sup>3</sup> Factors like family support, which include upbringing of the offspring, parent-child interaction and parental influence, and monitoring relationship characteristics, such as lack of relationship control, longer length of relationship, fear of condom use negotiation, less frequent partner communication about sexually related topics, and having older sexual partners, have been associated with greater likelihood of engaging in risk behaviors or acquiring sexually transmitted infections (STIs). Additionally date rape,

new partner and risky partner, peer influences and peer pressure to smoke, drink alcohol and engage in sexual intercourse also play a vital role. Social capital (an index comprised of trust, reciprocity, and cooperation among members of a social network) is inversely correlated with HIV/STIs acquisitions. Various aspects of community largely affect adolescent risk of STI acquisition. Communities that have high rates of STIs among adults may pose a heightened risk for adolescents. Sociological factors like poverty, low educational attainment, compromised family structures, and lower socioeconomic status are also important. The media and pornography indirectly have an important influence on the sexual health of adolescents. Adolescents may engage in risky sex or non-use of condoms due to lower level of perception of the risk for pregnancy and STIs. Multiple partners, lack of confidence in using condoms, inability to negotiate condom use with their partners, inability to say “no” to sexual intercourse not protected by a condom, belief that using condoms results in less pleasure, perception of low susceptibility to STI and HIV infection, inability to discuss sexual matters (i.e., previous partners, sexual histories), and current pregnancy all lead to a high risk of acquiring STIs. Psychological parameters like high levels of impulsivity, proclivity for sensation seeking behavior, alcohol or drug use, antisocial behaviors, low self-esteem, psychological distress, and depression further multiply the risk of acquiring STI in the adolescents. The shift toward later marriage in most countries has led to an increase in premarital sex, the prevalence of which is generally higher in developed countries than in the developing countries, and is higher in men than in women.<sup>4</sup> Sexual behaviors and the sharing of injection equipment that cause most HIV infections worldwide occur for many indulging motivations like desire, peer pressure, pleasure, physical or psychological dependence, self-esteem, love, access to material goods, obligation, coercion and force, habit, gender roles, custom, and culture.<sup>2</sup>

Advances in scaling up antiretroviral treatment in resource-poor countries, the benefits of male circumcision, and the hope for promise of pre-exposure prophylaxis and microbicides have made some difference; however, there is no simplistic solution to HIV prevention.



Behavioral interventions in HIV/STD prevention are a subject of considerable interest and debate. Two and a half decades ago no one would have thought that HIV prevention would be as difficult as it has proven to be. Despite efforts, UNAIDS now estimates that 33 million people are living with HIV, and 2.5 million new infections arise every year.<sup>2</sup> In the absence of effective vaccines behavioral interventions are the key to HIV/STD control strategies, but the question of what actually works remains a challenging one.<sup>5</sup> While biological science continues to unravel the secrets of the HIV, behavioral science has contributed much to our understanding of its prevalence, incidence, and distribution.<sup>6</sup> In the USA, studies on homosexual men show rapid reductions in high-risk behaviors and falling incidence of infectious diseases, including HIV, as the result of public health interventions.<sup>7-10</sup>

Dynamically changing demographic, economic, and cultural forces underlie the behaviors that directly determine the spread of STDs.<sup>11</sup> In many developing countries, additional social problems such as rapid population growth, rural to urban migration, work related travel, growing economic inequality between the rich and poor, low education and low status of women, political instability and wars all result in behaviors that fuel the hyperendemic transmission of STIs, with continuing epidemic spread of the newest STIs and HIV infection. Sociodemographic data and ethnographic research suggest progressive liberalization of sexual behavior during the 19th and 20th centuries, as a result of colonial and economic development, urbanization, population growth, and other factors.<sup>12,13</sup> Many societies especially developing countries however are still reluctant to openly address issues involving sex and sexuality and to recognize the realities of the widespread existence of pre- and extramarital intercourse.<sup>14</sup> This narrow minded attitude best explains the subsequent epidemic spread of HIV and other STIs.<sup>15</sup>

The HIV epidemic has been the single most important factor to both highlight the need for more systematic dissemination of information on sexual behavior and facilitate an enormous increase in infection related studies on sexual behavior.<sup>11</sup> It is now clearer than ever that sexual behavior is one of the most complex human social behaviors.<sup>16,17</sup> The term “sexual behavior” involves many components: sexual experience and activity, age at sexual debut or “coitarche”, current and life time number of sex partners, frequency of sexual intercourse, mode of recruitment of sexual partners, duration of sexual unions, and types of sexual practices.<sup>18</sup>

In a vast country like India, there are wide variations in geographical, cultural, and behavioral patterns.<sup>19</sup> Variations in sexual behavior patterns, even within a population influence the spread of STIs in that population. Linkages between sexual networks are necessary for the spread of STIs across these networks.<sup>20</sup> So called “core group” appears to be important in the spread of STIs and in their prevention. Core group refers to a small proportion of persons with an STI who transmit the disease, e.g., commercial sex workers (CSWs) and who sustain the endemic and epidemic transmission of STIs. Mixing between members of the “core” and the “periphery” affect the extent to which STIs spread to the general population. The sexual

transmission of STIs and HIV beyond core groups depends on persons who have sexual intercourse with members of the core group and then also with members of the general population and are called “bridge population”. Studies in Thailand revealed that large proportions of men in certain occupations such as truck drivers, the police, and the military tend to function as “bridges” between female sex workers and their wives or girl friends.<sup>21,22</sup> This pattern is observed in other diverse settings, particularly in Asia. In India, a high proportion of HIV positive persons are truck drivers who generally, acquire the infection from CSWs doing business on the highways leading to Mumbai or Chennai, 2 metropolitan cities of the Western and Southern zones of India, respectively. These long distance truck drivers through their high-risk sexual behavior contribute to the rapid spread of HIV infection. The transmission dynamics of STIs are influenced not only by sexual behavior but also by additional factors such as phase of the epidemic, population prevalence, transmission probability, duration of infectiousness, and specific characteristics of transmission networks.<sup>23,24</sup>

## What is Meant by Behavior?

Behavior is everything we think, do, and feel. It is not something, we are born with. We are born with temperament, physical, and sexual characteristics and these interact with our environment to produce our behavior and our habits. Behaviors take place over and over again until they become automatic and take place without the person having to think a great deal.<sup>25</sup>

Behavior is formed by a combination of 8 different factors: (1) The body and temperament we are born with which includes factors like intelligence, general health, physical appearance, handicaps, disabilities, talents, etc. (2) Gender which has an impact on what he or she does and what they are able to change, e.g., economic constraints on women, different values for male and female sexuality, powerlessness of woman relative to man, etc. (3) Culture greatly influences as particular cultural practices may help or hinder the patient’s ability to change, e.g., polygamous marriages, wife inheritance, rituals, cultural practices, and values about marriages, sexuality, child rearing, etc. (4) Religion plays an important role as the extent to which the patient’s religious beliefs help or hinder their attempts to change their behavior. (5) Economic conditions are vital as they help us understand whether the patient has ability to earn or have access to what he/she needs for survival. Do they have economic freedom to look ahead or make plans for the future? Do they have the economic resources for adequate healthcare and information? (6) Family and community which help shape the values, beliefs, and circumstances of patient’s social environment, and include friends, family, and sexual partners. Does the social environment offer support and assistance? Is the patient ostracized from his/her social environment because of his/her behavior? (7) Physical environment which helps determine whether the patient has adequate food, clothing, shelter, and water. How many people live in the same home? Under what circumstances? Is the area safe? (8) Personal factors like what are the personal resources or

weaknesses of the patient? Is the patient depressed, lonely, angry, or feeling overwhelmed? Does the patient have problem with drug or alcohol abuse?<sup>25</sup>

### What is Meant by Behavioral Intervention?

Various terms, including behavioral, psychosocial, and life style are used to describe very different kinds of interventions designed to change a wide range of human behaviors.<sup>5</sup> For example, the intervention may range from a brief exchange of information or advice to long term intensive psychological “counseling” or therapy. The aim of behavioral intervention may be to change behavioral patterns like smoking, exercise, dietary patterns or sexual behavior of individual(s), small “high risk” groups, or of communities as a whole. In the context of HIV/STIs prevention, a behavioral intervention is one that seeks to reduce the risk of acquiring or passing on HIV or other STIs by changing behaviors that lead to transmission of infection, principally sexual and injecting behaviors. This still encompasses a wide range of possibilities, even though the link between behavior change and transmission of infection may be fairly direct (for example, consistent use of condoms between known HIV discordant sexual partners) or much more direct (for example, raising self-esteem or negotiation skills among sexually inexperienced young people to reduce the likelihood of high-risk sexual behavior in the future).

National AIDS Control Organisation (NACO) has also recognized the role of educational and behavioral interventions. The 2nd National AIDS Control Program (AIDS II Project) has shifted its focus from raising awareness towards changing behavior through interventions, particularly for groups at high risk of contracting HIV.<sup>26</sup> Strategic plan gives primary importance to components of Information, Education and Communication (IEC). Information means news, data, facts, or knowledge. Education is the process by which people acquire knowledge, skills, habits, values, or attitudes. The word education is also used to describe the results of the educational process. Communication is sharing/providing information by speaking, writing, or other methods. It could be verbal (one way or two way) or nonverbal (body language—gestures, dress, behavior, eye to eye contact, facial expressions, messages on flip chart, flannel graphs, posters, billboards, flash cards, etc.). Probably, the most important type of communication is interpersonal or person-to-person communication, which happens when people make their thoughts and wishes known to one another. To sum up, IEC is a process that informs, motivates, and helps people to adopt and maintain healthy practices and life styles.<sup>25</sup>

### OBJECTIVES OF BEHAVIORAL INTERVENTIONS IN PREVENTION OF HIV/STIs

Goals for behavioral strategy involve spreading of knowledge, stigma reduction, access to services, delay to first intercourse, decrease in number of sexual partners, increases in condom use, and decrease in sharing of contaminated injection equipment.<sup>2</sup>

Although, sexual abstinence is a desirable objective,<sup>27</sup> programs must include instructions on safer sexual behaviors like<sup>14,27</sup>

1. reduction in the number of sexual partners,
2. avoidance of risky sexual practices,
3. where indicated, the consistent use of barrier methods such as condoms, and
4. a change towards appropriate healthcare seeking behavior, where infection is suspected.

Emerging risk groups such as young people, CSWs, mobile population and women (in whom the transmission of HIV virus to their children remains a major public health problem) should be targeted with behavioral interventions.

### STRATEGIES AND ACTIVITIES OF IEC<sup>26</sup> COMPONENT OF NATIONAL AIDS CONTROL PROGRAM

1. To raise awareness, knowledge, and understanding among the general population about AIDS and HIV infection, its transmission and methods of prevention.
2. To promote safe practices such as condom use, use of sterilized needles and syringes, use of safe blood through promotion of voluntary blood donation.
3. To mobilize all segments of the society to integrate AIDS messages and programing into existing activities.
4. To ensure that all relevant health workers are trained in AIDS communication and coping strategies.

It is now well-recognized by the authorities that the IEC activities in isolation are not effective. Therefore, the IEC has been integrated with the other components of the AIDS Control Program. Condom programing, STD services, and blood safety program carried out by well-trained health personnel, back the educational messages and information.

### BASIS OF BEHAVIORAL INTERVENTIONS

Behavioral interventions have been based on a number of psychological models such as theories of reasoned action,<sup>28</sup> self-efficacy,<sup>29</sup> and readiness to change.<sup>30</sup> Even though every behavior is unique, theories of behavioral prediction and behavior change suggest that there are only a limited number of critical factors (or variables) underlying an individual decision to perform or not perform a given behavior.<sup>31</sup> Behavioral science theories and research also suggest that the most effective intervention will be those which are directed at a specific behavior. Perhaps the most difficult part of developing any intervention is the identification of the behavior (or behaviors) that one wishes to change. The selection of a behavior (or behaviors) to serve as the target of an STI/HIV risk reduction intervention for a given individual, should be based on sound epidemiological evidence and a careful assessment of client's sexual and drug use history.<sup>32–36</sup> It is only by knowing the history that one can identify the one or two behaviors that are putting the client at greater risk for acquiring and transmitting HIV and other STIs. This behavior (or these behaviors) should serve as the target of an intervention.

Behavior change is usually not a one-step, all or nothing process but often involves a series of steps that ultimately may lead to long-term maintenance of a new behavior. Clearly, different behavior change messages will be necessary for a person who has not even thought about adopting a health-protective behavior than for a person who is trying to adopt that behavior.<sup>30,37,38</sup> By understanding the client's behavioral attitude, normative (patient's perceptions of what others think he/she should do), self-efficacy (patient's self-perceived ability to perform a target behavior), and beliefs, it should be possible to tailor a theoretically appropriate intervention.<sup>39</sup> Carefully designed theory based interventions that take into account the characteristics of the particular population or culture can cause positive changes towards preventing sexually risky behaviors but boundary conditions for their effectiveness still need to be identified.<sup>40</sup> Unfortunately, such theoretical considerations are often not taken into account in developing interventions.<sup>31</sup>

It is important to recognize that behaviors, even those which have been viewed as difficult or impossible to change (for example, sexual and drug using behaviors) can be changed and changed radically.<sup>31</sup> Moreover, it is also important to recognize that there are only a limited number of theoretical variables that influence and account for most of the variance in any given behavior. Generally speaking, once a person has formed a strong intention (or made a commitment) to perform a particular behavior, he or she is likely to perform that behavior given that the person has necessary skills and there are no environmental constraints to prevent behavioral performance. If not so, the healthcare provider can then determine whether failure to engage in protective behavior recurred due to lack of intention, lack of skills, or due to the presence of environmental constraints. If the failure is due to lack of intention, the provider can rapidly assess the client's behavioral, normative, and efficacy levels. Discussion of these beliefs along with the establishment of a risk reduction plan should help the client to change his or her behavior, thus reducing incidence of STIs.

### MATHEMATICAL MODELS IN THE ASSESSMENT OF THE IMPACT OF BEHAVIOR CHANGE

To better understand the role of behavior change and STI prevention as factors influencing HIV seroconversion, consider May and Anderson's<sup>41</sup> model of the reproductive rate of STIs. This model includes an equation for HIV:  $R_0 = \beta cD$ , where  $R_0$  indicates the reproductive rate of infection, typically interpreted as the expected total number of secondary infections arising from a single primary infection early in the epidemic when virtually, all individuals are susceptible.<sup>42</sup> When the reproductive rate is greater than one, the epidemic is growing; when  $R_0$  is less than one, the epidemic is dying out; and when  $R_0$  equals one the epidemic is in a state of equilibrium. Beta ( $\beta$ ) indicates transmission efficiency, or the ease with which an infected person can transmit the disease to an uninfected partner;  $c$  indicates the rate of partner change; and  $D$  indicates the length of time

a person is infectious.<sup>41–43</sup> Each of the parameters on the right side of the equation can be influenced by behavior or behavior change. For example, transmission efficiency ( $\beta$ ) can be reduced by increasing consistent and correct condom use or by delaying the onset of sexual activity; the rate of partner change ( $c$ ) can be influenced by decreasing the number of partners; and the length of time, a person is infectious ( $D$ ) can be influenced by increasing the likelihood that one will seek care at the first sign of symptoms. Biomedical interventions can influence transmission efficiency ( $\beta$ ) and the infectiousness ( $D$ ), whether one takes a biomedical or behavioral approach the impact of a change in any one parameter on the reproductive rate will depend on the values of other two parameters.<sup>41</sup> To complicate matters further, it must also be recognized that changes in one parameter may directly or indirectly influence one of the other parameters.<sup>43</sup> For example, some have argued that an intervention program that successfully increased condom use could also lead to an increase in number of partners, perhaps because now one felt safer. If this were the case, an increase in condom use or a reduced prevalence of STIs would not necessarily lead to a decrease in the reproductive rate. Condom use behaviors are very different with partners perceived as "safe" than partners perceived as "risky". Thus one should not expect to find a simple correlation between decreases in transmission efficiency and reductions in HIV seroconversion. Moreover, it should be recognized that many factors may influence transmission efficiency (e.g., degree of infectivity of the donor, characteristics of the host, type and frequency of sexual practices) and the variations in these factors will also influence the nature of a relationship between decreased STI rates, increased condom use and HIV seroincidence.<sup>44,45</sup>

These conclusions follow from other models of HIV transmission. For example, consider Reiss and Leik's<sup>46</sup> model of the probability of being infected with HIV.

$$p = 1 - [1 - \pi + \pi(1 - \phi\alpha)^{n/s}]^s$$

Where  $\pi$  indicates prevalence,  $\alpha$  indicates infectivity,  $\phi$  indicates condom failure probability,  $n$  indicates number of sex acts, and  $s$  indicates number of partners. Condom use is built directly into this model; moreover, the impact of condom use will depend on the degree of infectivity, the prevalence of the disease in the population, the number and type of sex acts, and the number of partners.<sup>43</sup>

Although this model, like the model proposed by May and Anderson,<sup>41</sup> clearly indicates that there is no reason to expect a simple relationship between a behavior change and reproductive rate of HIV, both models make different predictions about the effect of a behavior change.<sup>43</sup> Both behavior change and STI control can, under certain circumstances, help to reduce the transmission of HIV and other STIs. Although correct and consistent condom use can prevent HIV, gonorrhea, syphilis, and probably chlamydia, condoms are less effective in interrupting transmission of herpes and genital warts.<sup>47</sup> Thus, although one is always better off when using a condom than not using it, the impact of condom use is expected to vary with disease.<sup>43</sup>



## Approaches in Behavioral Intervention and Need to Develop STI Care Facilities

Population of the developing world have only limited awareness of the seriousness of STIs and of their signs and symptoms. Mass media can be used to raise general awareness, but a combination of mass media and interpersonal communication with approaches to modify community norms and provide supportive services, seems most promising to maintain safe behavior or to prevent and change behavior which is unsafe.<sup>48</sup> In addition, there is a need for sustained health promotion programs and education strategies targeted at specific groups which are at an increased risk of acquiring STIs. The content of health promotion messages should be appropriate and in general, options should be offered.<sup>14</sup> For young adolescents, for instance, the message could be to abstain from sexual intercourse until one is in a stable relationship or to explore nonpenetrative forms of intercourse; however, whenever penetrative sex takes place condoms should be used. Male condoms are undoubtedly effective in blocking HIV transmission, but female-initiated methods including physical barriers and topical antimicrobials (vaginal microbicides) need to be promoted because women and young girls account for most of those infected cases in countries where HIV is most prevalent.<sup>49</sup> Examples of specific groups that should be targeted with health education and health promotion approaches are STI patients and their clients, long distance truck drivers, street children, adolescents, and students. NACO has also adopted targeted intervention approach. These include special IEC approaches and provision of support services such as providing condoms and STI services. Some identified targeted population groups are injective drug users, migrant workers, industrial workers, military personnel, the commercial sex industry, street children, truck drivers, and slum dwellers. Educational interventions are useful tools for increasing knowledge and improving attitudes towards HIV infection. Secondary schools are equipped with the best environment for this purpose.<sup>50</sup> It is becoming necessary to carry out interventions among younger groups, as a greater impact is achieved.

Although proper medical treatment and providing adequate psychological and social support to adolescents who are already infected constitute an important aspect of the care, the solution lies in altering the behavior and practices that lead to the acquisition of these infections.<sup>51</sup> Under the auspices of NACO,<sup>26</sup> the Department of Youth Affairs and Sports, Ministry of Human Resources Development has taken up a number of activities to protect youth and to involve them actively in the AIDS prevention and control activities. These activities among youth are being implemented through a program named Universities Talk AIDS (UTA) by National Service Scheme. It is projected to reach all major universities and plus 2 level schools. In order to reach the rural areas, the department of Youth Affairs and Sports has organized many multimedia workshops using rural art forms. Plans are underway to tap large networks of youths like NCC (National Cadet Corps), YMCA (Young Men Christian Association), and YWCA (Young Women Christian Association),

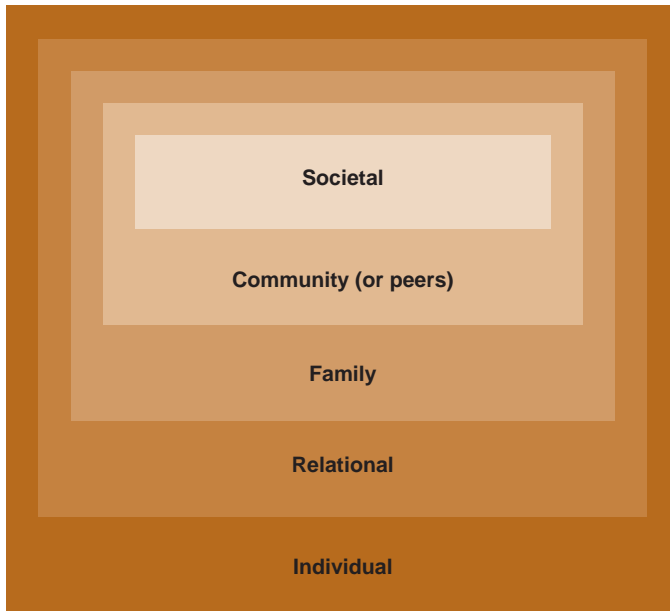
etc. It is also important that the necessary conditions are created for people to take the desired steps to prevent and control STIs.<sup>14</sup> For instance, where condoms are promoted for the prevention of STIs and HIV, good quality, affordable condoms should be readily available and where appropriate healthcare seeking behavior is promoted, good quality, effective, and acceptable services should be available to people with STIs. In developing countries, patients with STIs preferentially seek care in the informal sector for many reasons.<sup>52</sup> The major factor is cost, because the cost of care in the formal private sector is often prohibitive thus the informal private sector may be the only recourse that is open to them.<sup>53–55</sup> Inconvenient hours of operation, long waiting time and concerns about confidentiality and stigmatization all mitigate against seeking care in public clinics. Increased role of pharmacists and informal sector practitioners is being argued by some people, in the provision of STIs care.<sup>53</sup> Patients with STIs prefer the services provided by the informal sector not because these providers offer superior clinical treatment, but because they are accessible, provide medication (even if not efficacious) and involve no waiting time or judgemental treatment.<sup>52</sup> Improving the quality of STI services in the public sector is thus warranted. It is seen that number of STI cases attending STI clinics in government run hospitals are dwindling, however, HIV prevalence is increasing. This shows that attention needs to be given to this health field. In WP Kinsella's novel "Shoeless Joe", the building of an attractive base ball facility was sufficient to cause professionals and general public to flock to it ("If you build it, they will come"), however, this is not sufficient for STI services. Perhaps, the mantra should read, "If you build it and offer high quality, accessible, affordable, and nonstigmatizing STI care services, they will come".

### LEVELS OF INTERVENTIONS<sup>3</sup>

Although many individual-level interventions are effective, they may not be sufficient to sustain newly adopted STI-preventive behavioral changes over protracted periods of time or in the presence of countervailing influences. Effective interventions for behavioral modifications for the prevention of HIV and STIs can be delivered at multiple levels as discussed below (Fig. 10.1).

- **Individual level:** Emphasize motivational factors, provide skills training, including partner communication, sexual negotiation, resistance skills and condom application; and attempt to modify peer norms. Encourage greater participation in screening programs to identify particularly those who are asymptomatic.
- **Relationship level:** This is particularly important for adolescent females who are in power-imbalanced relationships with their male partners. "Adolescent-friendly" partner services represent an approach that may facilitate disclosure and promote care-seeking behavior of partners.
- **Family level:** Promote increased communication between adolescents and parents about STI prevention, increase parental monitoring of adolescents and perceptions of the adolescents regarding enhanced parental monitoring, foster a sense of increased family support.





**Fig. 10.1:** A socioecological model for STI risk and protective factors for adolescents.<sup>3</sup>

- **Community level:** Create social norms that promote safer sex practices. By evoking changes within the community in which adolescents are embedded, STI-preventive behaviors may be magnified. Effective use of adolescents' sexual networks as a venue for preventing and controlling STIs may become productive in the long run. Promoting, enhancing, or creating social capital is another community-based approach. It tries to influence the positive social networks so that the adolescents feel more connected, more supported, and are provided access to necessary resources such as extracurricular activities, condoms and sexual education through these enhanced support networks.
- **Societal level:** Mass media campaigns can be an effective tool for reaching adolescents who may not otherwise be exposed to interventions. Societal-level changes can also promote increased accessibility to and acceptability of STI prevention and control services for adolescents. Implementing policy initiatives such as adolescent partner notification and partner-delivered treatment may also be critically important.
- **A socioecological approach:** Effective STI prevention and control programs can best be achieved by "synergizing" these 5 levels of interventions (vide supra). STI-prevention resources should be linked into an efficient network. This network, for example, would consist of the community, schools, health providers, local government agencies, and nongovernmental agencies or community-based organizations. The role of this network would be to link resources thereby enhancing preventive services. For example, multiple access points (i.e., recreation centers, after school programs, and physicians' offices) could be used as opportunity sites for providing STI-

prevention information and motivating adolescents to adopt relevant health-promotion skills.

## Designing an Effective Educational/Behavioral Intervention<sup>56–60</sup>

Four main components of effective behavior change projects are

1. Information: Increase awareness and knowledge.
2. Social and self-regulative skills: Provide tools for effective prevention.
3. Guided rehearsal and corrective feedback: Enhance skills and self-efficacy in high-risk situations.
4. Social support: Aid and reinforce personal change efforts.

Various steps involved in designing such an intervention are

### Step 1: Assess the problem

- A. Identify one HIV/STI problem in your community that can be addressed by an educational behavioral intervention and describe it in as much detail as possible. Examples are poor attendance at the local STI clinic, inability of women who are seen at a particular STI clinic to recognize STI symptoms and obtain treatment in a timely manner, lack of access to condoms by sex workers in a particular brothel, higher prevalence of STIs and HIV among long distance truck drivers, etc. Who are the stakeholders? Who in the community is interested in solving this problem and what is their agenda? It could be hospital administrators, the target population, the government, or policy makers.
- B. What information do you need in order to quantify or define the problem, as it currently exists? How will you obtain this information? This will help you to establish a baseline for further evaluation of your intervention. This information can be obtained by key informant interviews (people who know the extent of the problem), from vital statistics records (e.g., deaths), surveillance data (e.g., numbers of people who have HIV/AIDS in a particular population), need assessment survey (sample your target population, could ask about knowledge, beliefs, practices, barriers to practice, very important to be as specific as possible when asking about practices), chart review, number of condoms purchased from the market, published literature, and so on. Are there any barriers to getting a fairly, accurate measure of this problem? What are they? Need to think about these barriers if key stakeholders want evidence of change that you can't deliver. They need to know this at the beginning.

### Step 2: Describe the audience or target population

It is essential to identify important groups that will need to be reached in the community. Different sections of public will have different information needs and will require separate and distinct approaches and messages. Possible target audience may be school children, school teachers, young persons (college and out of college youths), married couples, sex workers and their clients, patients at STI clinics, injecting drug users, homosexual

men, professional groups (e.g., health workers), traditional healers, quacks, religious and community leaders, employers and trade unions, parents, journalists, etc.

Describe the audience who will be targeted by this intervention by using factors given below. These factors will guide you to design your intervention. Please note that these are issues that you need to know about, but this does not replace the need to conduct an actual need assessment of the issues.

- A. Intrapersonal factors: They will include the knowledge, attitudes, beliefs, norms, culture, motivations, self-esteem, self-efficacy, and practices of the population that will support or impede them from making necessary changes. Readiness of this population to make change needs to be considered.
- B. Interpersonal factors: Under this, comes the social networks, social support, families, work groups, peers, neighbors, social norms, and other interpersonal factors that could help support or impede this population from making the desired change.
- C. Resources or lack of resources: They either support or impede this population's ability to make necessary changes. Potential barriers to access these resources also need to be understood.

### Step 3: Assess the organization

Assess the strengths of your organization and what it can contribute to developing the program to help solve the problem. What internal resources and support do you have (administrative support, staff, volunteers, expertise in treating patients for STIs, space, equipment)? What programs already exist that might be models for the program you want to develop? Think about what other organizations you would work with to carry out this program. How this program which you develop can best complement other existing interventions?

### Step 4: Write measurable and specific goals and objectives

- A. **Goal/outcome objective:** Outcome objective is a long-range goal, usually a quantitative measure of behavior or health problem. Setting realistic outcome objectives depends on having current baseline data. If rapid reduction in seoprevalence is not possible, slowing the rate of increase of HIV infection is a logical effective program.  
Set one goal or outcome you want to see. It happens as a result of the programs, you want to develop. This goal should be broad in scope. For example, to reduce further increase of HIV and STIs in long distance truck drivers at a given place at the end of 2 years of intervention.
- B. **Objectives:** These should be measurable objectives that will enable you to reach your goal.
  - i. **Program/process objectives:** "Process objectives" describe key activities essential to achieving the impact objectives. They are often used in pilot tests to determine changes needed before final production. They can be used as markers of progress.  
These "process objectives" describe the process you need to go through to develop and implement your

program. Examples are, putting together a planning committee by the end of 1999, hire all necessary staff by February 2000, sign agreements with all of the participating partners on the project by March 2000, carry out intervention by August 2000, etc.

- ii. **Learning objectives:** They are required to measure intended effect on an individual or group as a result of going through the program and perceived changes in how they think, feel, or behave after the program. Participants will be able to describe the ways in which HIV is transmitted, discuss how they feel about negotiating condom use with their partners, how they are encouraged to purchase condom in a drug store, and use them properly are some of the examples.
- iii. **Impact objectives:** Impact objectives are statements of the program's intended accomplishment in the immediate future. They are often a measure of knowledge, attitude, and behavior from survey and other methods.

These objectives describe the changes that can be observed as a result of the program. Examples are: 6 months after the program is initiated the number of condoms purchased in the specified area will increase by 25%; 6 months after the program is initiated, the number of women coming to STI clinic will increase by 15%; 3 months after the program, hospital policies will change to make it easier for providers to do STI/HIV counseling.

### Step 5: Choose educational models and methods

Which educational model and method or combination of models and methods are best suited to your problem. Examples of models are training course, training of trainers, peer education, mass media. Various methods that can be adopted are lecture, role-playing, demonstration, discussion, interactive exercises, video, brochure(s), or posters.

### Step 6: Implementation

Various components are

- A. Plan for securing speakers/trainers/other necessary staff/ putting together a planning committee. Be sure to include your target population as part of this committee.
- B. Plan for securing or developing educational materials.
- C. Plan for securing other training materials/equipment/ location.
- D. Plan for marketing your program.
- E. Develop a budget for your program.
- F. Develop a time line for your program (be realistic).

### Step 7: Assess effectiveness

It is important to consider the stakeholders and include them in the process of deciding what types of information they would like to have demonstrated to show that the program has been successful. Look at the different types of objectives that you have written; which of these objectives would you need to evaluate to satisfy the stakeholders? Some stakeholders may want you to

**Table 10.1:** Health Campaign Elements

1. Community strategies	—organizing, public relations, coalition building
2. Social control measures	—regulation, legislation, policy, taxes
3. Mass media	—print, electronic, broadcast, small media
4. Health services	—availability, access, funding
5. Economic factors	—removing barriers
6. Environmental factors	—removing barriers
7. Interpersonal approaches	—outreach, counseling, advocacy
8. Evaluation	—cost benefit, process, impact, outcome

demonstrate actual changes in STD rates in your community which are difficult to show in short term and, in addition, there may be other projects going on in your community that are working on the same problem that could also impact these rates.

Assess your program/process objectives (e.g., to show proof that staff was hired by the date you indicated), learning objectives (e.g., develop a pre-post test to determine if participants learned what you intended them to learn or you could observe what they have learnt) and impact objectives (e.g., count how many more patients have come into your STD clinic, do chart reviews, get an internal audit of condom purchases and how they have changed, show that you have a new policy in place).

Various elements of any health campaign are summarized in Table 10.1.

### STUDY DESIGNS IN ASSESSING EFFECTIVENESS OF BEHAVIORAL INTERVENTIONS

Considerable debate still centers on whether the randomized controlled trial should be considered the gold standard for evaluating the impact of behavioral interventions.<sup>61–64</sup> Despite considerable achievements, behavioral science is often viewed with skepticism by practitioners of biomedical science.<sup>6</sup> Studies that rely on “self reports” of participants and research designs that lack random assignment to isolated conditions are viewed as weaker than true experiments that incorporate biological markers as outcomes. However, traditional experimental methods are often hopelessly inapplicable to studies of risk behavior as practiced and are of limited feasibility in the evaluation of fledgling community public health programs. By contrast, the evidence based approach to the evaluation of healthcare interventions views the randomized trial as optimal research design for this purpose because of its ability to minimise bias and avoid false conclusions about what works and what does not. To accept the randomized trial as the gold standard, however, is not to deny its limitations and challenges, particularly in behavioral or psychosocial field.<sup>5,64</sup>

A frequent objection to randomized trials of behavioral interventions relates to the ethics of “with holding” the intervention from a control or comparison group.<sup>5,64</sup> Faced with the enormity of HIV epidemic and the urgent need to find effective behavioral interventions to combat its spread, there has been a tendency to think that action (implementing behavioral interventions) must be preferable to inaction.<sup>5</sup>

It has also been argued that randomized trials are not appropriate for evaluating behavioral interventions because they ignore the complexity of behavioral and psychosocial interventions.<sup>64</sup> Behavioral or psychosocial interventions are more likely to resemble a “black box”, in which the “active ingredient” has not been identified. Perhaps the greatest challenge, in the behavioral field, is to design and conduct trials in such a way that delivery of the intervention can be standardized as much as possible.<sup>5</sup>

### Behavioral Interventions and Outcome Measures in HIV/STI Prevention

Choice of outcomes by which to assess the success of a behavioral intervention is the key issue.<sup>45</sup> The ultimate goal of such intervention is to reduce the rate of new HIV/STIs in defined groups or populations, and many innovative interventions have been set up throughout the world with this goal in mind, but no randomized trial has yet reported the impact of a behavioral intervention on HIV incidence.<sup>61,65</sup>

Although most would agree that HIV seroincidence would be the strongest evidence used to assess the public health impact of HIV prevention studies, this assessment is often not possible if there is a low incidence of HIV in the population being studied.<sup>66</sup> Thus, many recommended that STIs should be used as surrogate markers for HIV, despite the fact that the true empirical relationship between a given STI and HIV has not been established. Under the circumstances, however, acute (non HIV) STIs are suitable end points for behavioral interventions trials because they are important causes of morbidity in themselves, they occur more commonly than HIV infection, and have been clearly shown to increase the risk of HIV transmission.<sup>67,68</sup>

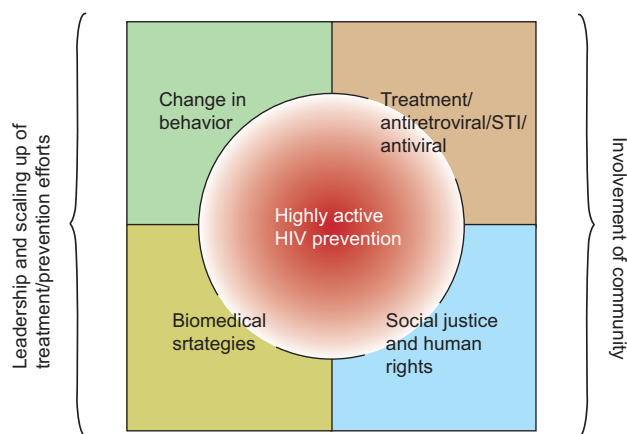
By analogy, the success of a behavioral intervention trial may be influenced by rapidly changing social and community norms in relation to sexual behavior. Changing sexual behavior through specific interventions is no easy task, and experience in other fields suggests that we should not expect big effects, as experimental interventions encompass only a segment of what social movement brings to bear.<sup>5,69</sup>

It will be useful to assess the effects of a behavioral intervention on both behavioral and biological outcomes.<sup>43</sup> Even in the absence of biological measures, behavioral self reports can provide useful information about the efficacy and effectiveness of behavior change interventions.

### LIMITATIONS OF BEHAVIORAL INTERVENTIONS AND NEWER APPROACHES

Studies have shown that behavioral interventions alone did not produce any satisfactory decrease in the pandemic spread of HIV. An integrative package that includes biomedical, behavioral, and structural interventions offers the best method of preventing HIV spread. The combination of multimodal prevention strategies are needed to maintain adherence, to avoid sexual disinhibition (risk compensation), and are essential for





**Fig. 10.2:** Highly active HIV prevention.<sup>2</sup> (This term was coined by Prof K Holmes, University of Washington School of Medicine, Seattle, WA, USA).

addressing mechanisms that will scale up the optimized effects. The biomedical interventions that are effective in prevention include use of male condoms; male circumcision; and prophylactic use of antiretroviral drugs or contraception to prevent unwanted pregnancies and to reduce mother-to-child transmission. Oral and vaginal antiretroviral drugs both for pre-exposure prophylaxis and to reduce infectiousness among HIV-positive individuals are being assessed. Female-initiated methods, including physical barriers and topical antimicrobials (vaginal microbicide) products should be promoted.<sup>49</sup>

For the past two and a half decades, HIV prevention has been dominated by individual-level behavioral interventions that seek to influence knowledge, attitudes, and behaviors, such as promotion of condom use, or sexual-health education, and education of injecting drug users about the dangers of sharing equipment. Individual-level behavioral interventions have been successful to a limited extent, and it has shown that structural interventions substantially improve the outcomes of such a strategy. Structural interventions refers to addressing social, economic, political, and environmental factors (like poverty and wealth, gender, age, policy, and power that eventually shape or constrain individual behavior) and seek to change the root causes that affect individual risk and vulnerability to HIV. These are long-term initiatives that belong within the purview of broader economic and social development.<sup>70</sup>

Thus, the realm of “highly active HIV prevention” can be conceptualized as shown in Fig. 10.2.

## Conclusion

Research on HIV prevention during the past decade has identified numerous models, at levels ranging from individual interventions to public policies capable of affecting an entire population.<sup>71</sup> None of these approaches should be considered sufficient in itself because, put simply, it is well-known that behavior is difficult to modify. This truism is especially applicable when the behavior is determined by many factors and serves many needs, as is the case

with sexual behavior. Therefore, each of these approaches should be seen as one part of a comprehensive HIV/STI prevention program. Such efforts need to target individuals, small groups, communities, schools, and social policies. Adoption of theoretically guided and empirically validated approaches promises most success. There remains an urgent need to develop and tailor HIV prevention approaches that can promote the maintenance of behavior change, to reach community segments that remain vulnerable, and to address the changing context of the epidemic.<sup>72</sup> Finally, the fundamentals of HIV prevention need to be agreed upon, funded, implemented, measured, and achieved in a comprehensive and sustained manner.<sup>2</sup>

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# 11

## Condoms and Other Barrier Methods of STI and HIV Prevention

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### Introduction

This chapter will briefly review what is known about the effectiveness of condoms against sexually transmitted infections (STIs), including HIV. The chapter will then provide an in-depth examination of the behavioral and political issues that ultimately create challenges to condom use promotion thereby mitigating the ability to easily prevent infections. Novel interventions designed to promote the consistent and correct use of condoms will be reviewed. Subsequently, the chapter will review several barrier method alternatives to condoms, with an emphasis on the emergence of vaginal microbicides.

### Condom Effectiveness

In the year 2001, the United States Department of Health and Human Services issued a report on a workshop designed to assess the effectiveness of latex condoms for the prevention of STIs.<sup>1</sup> The report cited evidence that condoms are effective in preventing HIV transmission and female-to-male transmission of gonorrhea, but stated that empirical evidence was insufficient to evaluate the degree of risk reduction provided by condoms in regards to chlamydia, trichomoniasis, syphilis, chancroid, genital herpes, and human papillomavirus (HPV). An unfortunate outcome of this report was that opponents of safer sex programs interpreted the lack of evidence to mean that condoms do not work rather than simply concluding that the evidence had not yet been collected. While considerable controversy followed this report, the critical implication did indeed involve the need for further research on condom effectiveness. As the report noted, “to definitively answer the remaining questions about condom effectiveness for preventing STI infections will require well-designed and ethically sound clinical studies.”

In the years that followed the report, several studies were published that either provided further evidence of condom effectiveness, critiqued the methodology of the panel generating the report, or provided methodological guidance for further studies of condom effectiveness.<sup>2–10</sup> Further, the National Institutes of Health (US) funded a large multisite, prospective,

evaluation of condom effectiveness against biologically assessed nonviral STIs.<sup>11</sup> While more studies are still needed, two realities are apparent: (i) methodological issues inherent in the study of condom effectiveness have consistently created a bias toward the null<sup>4–6,9,10</sup> (meaning that results unfairly favor the hypothesis that condoms are not effective), and (ii) it has become apparent that the consistent and correct use of latex condoms offers considerable protection against most STIs, including even HPV<sup>8</sup> and genital herpes.<sup>7</sup>

To summarize the evidence briefly, the panel of experts commissioned for the 2001 report evaluated 138 published studies that provided evidence regarding the effectiveness of condoms against HIV and seven other STIs.<sup>1</sup> Only studies reporting evidence pertaining to the transmission of STIs through penile-vaginal sex were reviewed. The panel agreed that the quality of male (latex) condoms was very high and that *in vitro* evidence supporting a potential protective effect was strong. Indeed, *in vitro* assays have consistently shown that the porosity of condoms is protective against even the smallest sexually transmitted pathogens (e.g., viral STIs, including HIV).<sup>12</sup> Although the panel concluded that condoms do prevent female-to-male transmission of gonorrhea, they noted that evidence was (at the time) insufficient to judge the adequacy or inadequacy of condoms for the prevention of male-to-female transmission of gonorrhea and for the prevention of six other STIs. Evidence regarding condom effectiveness against HIV acquisition and transmission was very strong—primarily because of rigorous studies among serodiscordant couples<sup>13,14</sup>—thus, the panel concluded that consistent and correct use of latex condoms is highly protective against HIV infection. Beyond the US report, studies have provided evidence of condom effectiveness against chlamydia<sup>15–17</sup> and male-to-female transmission of gonorrhea.<sup>17–20</sup> At least one study provided evidence suggesting that condoms are protective against trichomoniasis.<sup>17</sup>

Although much more research remains to be conducted regarding condom effectiveness (especially relative to penile-anal sex and penile-oral sex), it is quite fair to say that the current need is to precisely quantify the degree of protection

offered by condoms rather than debating the specious question of whether or not condoms work at all. In addition, and more importantly, sufficient evidence supporting condom effectiveness against various STIs has accumulated to warrant the expansion of condom use research into the intricacies of behavioral research.

## Behavioral Research

In this section of the chapter, we address key behavioral issues pertaining to the use of condoms. For convenience, the issues are divided into (i) use of condoms, and (ii) correct use.

### PROMOTING THE USE OF CONDOMS

Much data exist on the prevalence of condom use among adolescents and young adults. Recent data indicate that condom use has been increasing over time among US adolescents. For example, national surveys indicate that condom use at last intercourse increased from 46% in 1991 to 62% in 2007.<sup>21,22</sup> While hormonal birth control use has remained unchanged over that same period of time, the prevalence of condom use increased during 1991–2003 and then leveled off during 2003–2007. These increases have been detected in all major racial/ethnic groups, including African-American, Hispanic, and white adolescents.<sup>21,22</sup>

Consistent condom use also appears to be increasing with the passage of time. Where surveys of US adolescents have tended to find rates of consistent condom use to be below 50%,<sup>23</sup> recent data suggest that rates of consistent condom may now be in the 50%–80% range (15–19 year olds).<sup>22</sup> These and other data also indicate that condom use is higher among males than females and higher among African American adolescents as compared with white and Hispanic adolescents.<sup>21,22,24</sup> National studies have also found condoms to be used more among higher risk populations, such as those with multiple sexual partners.<sup>25,26</sup>

Studies of young adults suggest lower rates of condom use than that of adolescents. It should be noted, however, that data on young adults are not as recent due to the fact that surveillance surveys in the United States tend to be conducted with adolescents or adults. Nationally representative studies of young adults have found rates of consistent condom use among sexually active 18–29 year olds to be as low as 7%<sup>27</sup> or higher at 16% or 24%.<sup>28</sup> A large survey of undergraduate college students found 88% to be sexually active but only 18% to use condoms consistently.<sup>29</sup>

A rather robust finding in studies of condom use is that individuals are more likely to use condoms with secondary or casual sex partners than with main or steady partners. For example, while Anderson and colleagues found 62% of individuals to use condoms at last intercourse with secondary partners, only 19% were found to use condoms with main or steady sexual partners.<sup>24</sup> This finding has been replicated across numerous populations, including heterosexual and homosexual adolescents and young adults, injection drug users, and commercial sex workers (CSWs).<sup>5,29,30</sup> This phenomenon appears to be the result of individuals having vastly differing perceptions of risk of the

two types of partners.<sup>31,32</sup> In fact, a recent study of 1489 young adults<sup>32</sup> illustrates this point. In this study, young adults were asked to rate the likelihood that an individual would get an STI or get pregnant if they had unprotected sex with a main/steady versus casual partner. No differences were found on pregnancy, as young adults reported a high likelihood that unprotected sex would lead to pregnancy with both types of partners. In contrast to this, whereas 80% of the sample reported that it was likely that unprotected sex with a casual partner would lead to an STI, only 33% of the sample reported this for a main/steady partner.

Research has suggested that a variety of psychological processes within intimate and sexual relationships play into the perception that main/steady partners are automatically safe partners.<sup>5,29,30</sup> In particular, factors that can impede condom use in main partnerships include trust and intimacy. While trust is generally a positive dimension within intimate relationships, in the sexual context it can undermine condom use.<sup>33–35</sup> For example, the *contraceptive switch* (discussed more below) that some couples make when they go from condoms to hormonal birth control is seen as an intimate and trust-building step in both adolescent and young adult relationships.<sup>33,36</sup> Some studies have further found an association between trust and commitment-related beliefs and condom use. For instance, the belief that asking a partner to use condoms means you are implying they are unfaithful,<sup>35,37</sup> and the belief that losing a partner may mean losing additional friends and family<sup>38</sup> have both been found to be related to lower rates of condom use. Perceptions of greater relationship quality and intimacy have been associated with lower rates of condom use in several studies of adolescents.<sup>39–41</sup>

Moreover, in some cases, adolescents engage in unsafe sexual practices with their main partner to demonstrate trust.<sup>34</sup> In addition, in the context of a close relationship, studies have found condoms themselves to be perceived as representing *mistrust*, and their very presence can arouse suspicions of cheating.<sup>28,35,37,42</sup>

Another important issue in this area has to do with how condom use changes over time in relationships. Ku and colleagues has proposed the *sawtooth hypothesis*, which posits that within a close relationship, condom use will vary over time, with the direction of condom use decreasing and creating a *sawtooth* pattern.<sup>43</sup> Using data from the National Survey of Adolescent Males (NSAM), they demonstrated that condom use tends to be highest at the beginning of a relationship and decrease over the course of a relationship. Specifically, they reported that 53% of young men used condoms at initial intercourse with their close partner, whereas only 44% used condoms with that same partner at their most recent intercourse occasion. In addition, use of other contraceptive methods followed the reverse path. Namely, only 29% of young men's partners used birth control (other than condoms) at initial intercourse with their close partner, whereas 48% used birth control with that same partner at their most recent intercourse occasion. Other researchers have found support for the notion that as relationships progress, condom use diminishes.<sup>38,41,44</sup> These and other data support the notion of the *contraceptive switch*, or the idea that partners



start off using condoms, and then as the relationship progresses move to a hormonal contraceptive method such as birth control pills.<sup>33,36,43,45</sup> The implication here is that once a couple has been together for a period of time, they no longer view one another as a potential STI risk. Switching from condoms to birth control pills, while perhaps viewed as more convenient for the couple, leaves the couple unprotected from STIs that one or one's partner may have.

Interestingly, studies suggest that the period of time that elapses before condom use begins to diminish is rather short. Fortenberry and colleagues reported, in a longitudinal study of adolescents and young adults, that condom use stopped in most relationships at approximately 3 weeks after initiation of sex.<sup>44</sup> This suggests that the perceptions of a new or casual partner change to perceptions of a main/steady partner within a relatively short period of time.

A large literature also demonstrates the importance of both belief systems and skills to the enactment of condom use among adolescents and young adults. Youth are more likely to use condoms if they have positive attitudes toward them and they perceive that others in their peer group also use condoms.<sup>46,47</sup> One particularly salient belief, especially among men, is the belief that condoms reduce sexual pleasure. Numerous studies demonstrate that those who hold this belief are less likely to use condoms than those that do not hold this belief.<sup>47,48</sup> It is for this reason that intervention programs to increase condom use often emphasize the eroticization of condom use,<sup>49</sup> in attempts to make condoms more erotic and acceptable in sexual encounters.

Moreover, data indicate that one of the strongest psychosocial predictors of condom use is condom self-efficacy,<sup>47,50</sup> or the perceived ability to use condoms in a variety of situations. Those who have high self-efficacy (or confidence) are able to use condoms even in challenging situations, such as when they are under the influence of alcohol or drugs, when they perceive the risk of a partner to be low, or when they get caught in the "heat of the moment."<sup>51</sup> Unfortunately, low self-efficacy may lead to unprotected sex even when an individual had intended to use condoms.<sup>52</sup> Skills training to address strategies for enhancing self-efficacy are often taught in HIV prevention interventions in efforts to boost participants' condom self-efficacy.<sup>50</sup>

Finally, studies have demonstrated that communication and negotiation skills are critical to the enactment of condom use.<sup>53</sup> In fact, self-reported partner communication about condom use is one of the strongest predictors of actual condom use.<sup>47,54</sup> In many ways this is not surprising, since it is often necessary for one individual (often the female) to communicate a desire to use condoms with a sexual partner (often the male). In the absence of good communication and negotiation skills, condom use may not take place.<sup>53</sup> Moreover, this is another focus of preventive interventions, in that numerous HIV prevention interventions teach individuals how to bring up the topic of safer sex as well as how to negotiate condom use with a resistant sexual partner.<sup>55</sup>

Given the strong associations of many of these psychosocial variables to condom use, a number of behavioral theories (that

contain these variables) are often used as bases for HIV prevention behavioral interventions.<sup>56</sup> Although each theory differs in various ways, most contain a set of similar psychosocial variables.<sup>57</sup> One popular theory, which summarizes such variables in a parsimonious fashion, is the information-motivation-behavioral skills (IMB) model.<sup>58</sup> This theory suggests that whether an individual will engage in condom use is a function of three factors: (i) a person's knowledge about HIV prevention practices and condom use; (ii) a person's motivation to engage in condom use, including their perceptions of risk of STI/HIV, their attitudes toward condoms, and their perceptions of social norms about condom use; and (iii) a person's behavioral skills for enacting condom use, such as perceived self-efficacy and condom communication and negotiation skills. The IMB model suggests that a person must have the knowledge, motivation, and skills to effectively enact condom use in sexual situations, and such a model helps us understand why individuals with only the knowledge (but not the motivation and/or skills) fail to engage in safer sex. Given this proposition, scores of behavioral interventions have been based upon the IMB model and/or similar behavioral theories, in efforts to affect these psychosocial variables and ultimately impact condom use.<sup>57,58</sup> Reviews and meta-analyses of such intervention programs suggest that such behavioral interventions are generally efficacious in increasing condom use and affecting other sexual risk behaviors.<sup>59,60</sup>

Of course, one of the most important behavioral issues relevant to condom use involves patients of STI clinics. A critical question for clinicians working in clinics that diagnose and treat STIs is whether patients are more likely to use condoms after being diagnosed with an infection. A recent study evaluated this question with respect to a new diagnosis of HSV-2 infection.<sup>61</sup> In a 3-month prospective study of men and women attending an STD clinic in the US, 43.4% (111 people) of those completing follow-up questionnaires, tested positive for HSV-2 at enrollment. Significant differences (assessed at follow-up) between persons testing positive and persons testing negative were not found for frequency of condom use. When analyzing change (baseline to follow-up) among only those testing positive, significant differences were not found with the exception of reporting greater frequency of condom use with steady ( $p = 0.037$ ) and non-steady partners at follow-up ( $p = 0.017$ ).

A final behavioral issue, and perhaps the most substantial, involves the observation that is all too obvious—this method of disease prevention is simply not acceptable to women (or couples) desiring conception. In many settings, sociocultural expectations for married couples, such as the assumption of monogamy in marriage or societal pressure to conceive, do not encourage condom use in married relationships. Indeed, worldwide, condom use among married couples is low.<sup>62</sup> This is unfortunate considering that in many regions heterosexual sex with one's husband has become a major HIV risk factor for women,<sup>63–68</sup> implying that husbands acquire STIs or HIV in extramarital relationships and then infect their wives. Of course, either spouse may engage in extramarital relationships

and present potential STI/HIV risk to their partner, but in many countries, married men are more likely to engage in premarital or extramarital sex because it is more acceptable for or expected of them.<sup>69–73</sup> Thus, the role of condoms in the prevention of STIs and HIV in married relationships has become an important focus and one heavily nuanced by a culture's gender norms and views on sexuality.

In South Asia, for example, condom use is often identified with contraception.<sup>74</sup> Married women in this region are under considerable pressure to demonstrate fertility and to bear sons.<sup>75,76</sup> In India and Bangladesh, where the birth of sons secures a woman's social and economic position,<sup>77,78</sup> the use of condoms in a married relationship interferes with this goal, and therefore, with the woman's realization of her culturally sanctioned gender role.<sup>74</sup> Research in China indicates that married couples at risk for STIs and HIV (couples in which the husband is a migrant worker) are less likely to use condoms when the wife is using an alternative contraceptive method.<sup>79,80</sup> In fact, in one study, 80.1% of women responded that their use of another form of contraception was reason for not using condoms.<sup>79</sup> In a qualitative study among married women in Uganda, women report using the contraceptive quality of condoms as a persuasive strategy to introduce condom use to their husbands. In these strategies, women would emphasize that their bodies could not handle other contraceptive methods, or they would cite economic reasons for using condoms as a family planning method. Further, women explained that identifying condom use in their marriage as specifically a contraceptive measure helped to deflect feelings of distrust the introduction of condoms would have otherwise generated.<sup>81</sup>

Indeed, research in a variety of settings finds condom use introduces distrust, suggests marital infidelity, and is identified with promiscuity or sex work, leading some scholars to say that the significance of condoms to feelings of trust and intimacy in a relationship is the central influence on decisions about whether and when a couple uses a condom.<sup>82</sup> Evidence of the condom's interference with intimacy and feelings of fidelity can be found in qualitative research in Malawi. According to data from more than 300 participant diaries, condom use represents risky, less serious, and less intimate relationships. Therefore, even when participants believed condom use to be appropriate, wise, or even a matter of life and death, the capability of condoms to define relationships ultimately determined whether or not a condom was used.<sup>83</sup>

Similarly, in India, condoms are widely perceived as necessary only to prevent pregnancy and infection during sex with CSWs.<sup>72,84</sup> Accordingly, a spouse's suggestion of condom use could make a strong statement against the wife's virtue, raise suspicions of the husband's fidelity, or suggest either spouse is infected with an STI or HIV. This perception may also discourage the purchase of condoms in that people buying condoms may be seen as seeking sex with sex workers.<sup>74</sup>

Most HIV prevention and treatment services currently deal with patients as individuals rather than as members of a married partnership, and interventions promoting condom use in marriage

are few. Research in sub-Saharan Africa, however, indicates that voluntary counseling and testing programs followed by behavioral-change interventions aimed at couples have been shown to reduce HIV transmission among serodiscordant married and cohabiting couples.<sup>85–87</sup>

Also of great importance is the observation that once pregnancy (planned or unplanned) occurs couples are prone to abandon any condom use that had been practiced before conception. In one study, for example, pregnant adolescents compared to their nonpregnant counterparts, reported less overall condom use, more infrequent condom use, and more unprotected vaginal sex.<sup>88</sup> In that same study, pregnant and nonpregnant adolescents were equally likely to test positive for STDs and equally likely to self-report having STDs during a 12-month follow-up period. These findings (and those from other studies)<sup>89–91</sup> suggest that pregnant adolescents may be less likely to use condoms than their nonpregnant peers and that STD incidence among pregnant adolescents may be high even though they are potentially receiving prenatal care. Clearly then, condom use promotion may be critically important as part of adolescents' prenatal care. This is particularly true with respect to those having sex partners known to be infected with genital herpes. Indeed, testing negative for HSV-2 during the first prenatal visit represents a clinical opportunity for counseling and education designed to decrease adolescents' risk of primary HSV-2 infection during the remainder of the gestation period. Evidence suggests that condom use may protect women from HSV-2 acquisition.<sup>92</sup> Given that a substantial portion of neonatal HSV is caused by HSV-1, adolescents could also be counseled to avoid cunnilingus during pregnancy.

An important point about condom use that should also be kept in mind is that heterosexual couples often have a difficult time of achieving condom use when the female partner is using hormonal contraceptives. This is most likely a result of a mismatch between the perceptions of pregnancy likelihood compared to the likelihood of disease transmission. Whereas conceiving is viewed as normal and even a sign of vitality; disease is viewed as an unlikely event given the apparent good health of each partner. In essence, pregnancy prevention may be the primary motivating force behind the use of condoms and once a better method comes along (e.g., hormonal contraceptives) couples may be quick to discard the practice of condom use. This all too common dynamic has spawned research investigating factors that may best be altered to promote the dual use of condoms and hormonal contraceptives.<sup>93–96</sup>

## PROMOTING THE CORRECT USE OF CONDOMS

A nagging question that frequently came up in studies that involved the use of condoms and also assessed incident STDs is, "How is it possible for consistent users to be diagnosed with STDs such as gonorrhea, chlamydia, and trichomoniasis if indeed condoms confer protection." A good example was published by Zenilman and colleagues in 1995.<sup>97</sup> They observed a lack of association between condom use and incident STDs that may

indeed been a consequence of unmeasured confounding. More specifically, the study did not assess whether condoms broke, slipped off, were applied after sex had begun, or were removed before sex was concluded. A subsequent paper published by Crosby and colleagues reported a similarly puzzling finding from a study of adolescent females. Among those reporting 100% condom use, 17.8% tested positive for at least one of three STDs (gonorrhea, chlamydia, or trichomoniasis).<sup>98</sup> A subsequent paper (based on a different sample of adolescent females) demonstrated that by accounting for “fatal errors” in condom use a nonsignificant association between condom use and STDs achieved significance.<sup>10</sup> The unadjusted measure of unprotected vaginal sex was not significantly associated with biologically-confirmed prevalence of STDs (Prevalence Ratio [PR] = 1.51; 95% CI = 0.71–3.21;  $p = 0.28$ ). Alternatively, the adjusted measure achieved significance (PR = 3.59; 95% CI = 1.13–11.38;  $p = 0.014$ ). More than one-quarter (25.6%) of teens using condoms inconsistently and/or incorrectly tested positive for an STD compared to 7.1% among those reporting the consistent and correct use of condoms.

Fifteen years after the study published by Zenilman and colleagues,<sup>97</sup> it is now widely apparent that people make multiple errors when using condoms and that they experience an array of problems; many of which may lead to condom failure and may discourage continued use of condoms. For example, a study of condom-using men found that 43% reported recently putting a condom on after starting sex and 15% recently reported taking a condom off before sex was over.<sup>99</sup> The study also found that 30% placed the condom upside-down on the penis and flipped the condom over before starting sex (thereby potentially transferring infected seminal fluid to the exterior of the condom). In addition, the study identified and assessed four likely problems or outcomes of these errors, including slippage and breakage (reported by 35%). A subsequent study reported remarkably similar findings for condom-using women<sup>100</sup> (including a specific analysis of those who applied condoms to their male partners).<sup>101</sup> Indeed, frequent condom errors and problems for both men and women have been reported by several research teams.<sup>102–107</sup> For example, it is possible that “incomplete use” of condoms is quite common.<sup>100,103–105</sup> This occurs when condoms are applied after penetration or removed before withdrawal.

Avoiding user errors in condom use is critically important to the control and prevention of STDs. For example, incomplete use may be based on the event of ejaculation. That is, the condom may be used only immediately before and during ejaculation. It is also conceivable that incomplete use is associated with perceived erection problems.<sup>108–110</sup> Two problems (breakage and slippage of condoms) are, of course, critical concerns. Thus, an important sub-question is, “What are the errors that lead to condom breakage?” and “What are the errors that lead to condom slippage?”

A study of men attending an STD clinic provided some initial evidence suggesting reasons why condoms may break during penile-vaginal sex.<sup>111</sup> Each of 278 men provided reports about the last 3 times they used condoms thereby creating 834 observations.

Men reported breakage during 125 of these occasions, making the breakage rate 15.0%. Eighty-seven men (31.3%) reported breakage during at least one of the 3 occasions of penile-vaginal sex. Men who reported a previous history of STI were about twice as likely as those reporting they had never had an STI to report breakage. In multivariate analyses, men who reported problems with condom slippage were about 2.5 times more likely to also report breakage. In addition, men with relatively lower self-efficacy to use condoms correctly were about twice as likely to report breakage. Three primary causes of breakage were identified. Men who reported that condoms had contacted a sharp object were about 2.6 times more likely to report breakage than men saying condoms did not contact sharp objects. Also, men reporting problems with the “fit or feel” of condoms were about 2.3 times more likely to report breakage than men not having this difficulty. Finally, men reporting that they had not squeezed air from the receptacle tip were about twice as likely to report breakage. Although more investigation regarding why problems with “fit and feel” may cause breakage is needed, some evidence suggests that tight fitting condoms may be the link between “fit and feel” problems and breakage.<sup>112–116</sup> In another study of men, those who had used an oil-based lubricant were more than 3 times as likely to report breakage and those who completely unrolled the condom before putting it on were also about 3 times more likely to report breakage.<sup>117</sup> Of course, it is quite likely that other potential causes of condom breakage will be identified; however, the overarching conclusion is unlikely to change: condom breakage may be averted through the improved selection (for fit) and application of condoms.

In a study that combined the events of condom breakage and slippage,<sup>118</sup> it was observed that men who report that their partners were not “highly motivated” may be more likely to report condom breakage/slippage. Higher number of partners and more frequent condom use were associated with condom breakage/slippage. Finally, men who had never been instructed about correct condom use were about twice as likely to report breakage/slippage as compared to those indicating they had received this form of instruction. Unfortunately, only a handful of studies have specifically investigated the possible causes of condom slippage. One, for example, used an event-level analysis (meaning that the measures used all pertained to the same act of sex) and found that slippage was about 5 times more likely among men reporting they had used phosphodiesterase type 5 inhibitors (erection enhancing drugs) when having sex.<sup>119</sup> The reasons why prolonged erection from these drugs may lead to slippage are not known at this time. However, it is increasingly apparent that erection issues and condom slippage are related. For example, a study of college students found that those who reported at least one instance of erection loss *during condom application* (just over 1/7 of the sample) were more than twice as likely to report that the condom had slipped off. Also, those who reported at least one instance of erection loss *during sex* (just over 1/6 of the sample) were more than 4 times as likely to report slippage.



The same study also found that slippage was more than twice as likely when lubrication of the condoms was poor.<sup>119</sup>

Of course, one of the best ways to truly appreciate the issues surrounding the correct application, correct use, and enjoyment of condoms is to consider findings from qualitative studies. For example, in a recent qualitative study of African American men (conducted by the first author) newly diagnosed with a sexually transmitted disease (STD), one theme that emerged was that men did not exercise unilateral control over condom use.<sup>119</sup> This is an important observation as it often assumed that men are completely able to control whether or not condoms are used. Evidence does suggest that the quality of condom use is also greater when both the male and female partner in a heterosexual relationship make the decision to use condoms on a mutual basis.<sup>120</sup> Men in the qualitative study also described condoms as physically detracting from sex and simultaneously enhancing the experience through the relief of anxiety pertaining to disease and pregnancy. One man, for instance, stated, “It (condom use) was better for my mind but to my body it was worse.” Another man stated, “I’m starting to enjoy using a condom even though there’s nothing like natural sex...but with all of these diseases...” Despite perceptions about the added mental pleasure from condom use, men were nonetheless clear about the loss of physical sensation. For most, however, the trade-off between “peace of mind” and loss of skin-to-skin contact seemed worthwhile. One man provided an extremely interesting perspective: “I think personally that when you use a condom you can go longer.” Findings from another qualitative study<sup>112</sup> also make some of the condom use errors and problems quite salient. For example, regarding condom lubricants one young man stated, “It (baby oil) suites me better—it creates more slip and slide.” Another stated, “If it (the condom) dries out I usually put lotion on or whatever I can find.” Regarding condom availability, one quote seemed to describe the sentiments of many men: “Late at night you don’t have time to look around—you use what you can get.” Although a vast number of other condom use issues could be examined qualitatively in this chapter, the important point to bear in mind is a simple one: condom use (unlike sex) is a learned set of actions that are seldom taught to people, hence the knowledge and skill levels of vast numbers of men and women are inadequate to achieve condom use that is not only correct (mechanically) but also enjoyable. It is also vital to keep in mind that condom use is only a small part of a much larger behavior—sexual intercourse. The sexual rituals and “rules” that couples follow when they have sex may have a much larger influence on their condom use behavior than is realized. With each new partner and with each established partner the process of negotiating for condom use and actually using condoms may shift and change as function of the relational and sexual dynamics. Indeed, this observation may explain a rather robust finding that incorrect condom use is more likely to be reported by men having multiple sex partners.<sup>122</sup>

## CRITICAL EMPIRICAL GAPS REGARDING CONDOM USE

Unfortunately, the empirical literature base relative to condom use has developed with a strong bias toward penile-vaginal sex thereby neglecting research studies evaluating the behavioral issues relative to condom use during oral and anal sex. Very little, for example, is known about the use of condoms for oral-genital sex among couples (gay or straight). One fairly robust observation has been that condom use for oral sex is extremely rare.<sup>121,123,124</sup> In a study of college students, 80% of those engaging in oral sex had never used a condom even though they were knowledgeable of the STD risk associated with oral sex.<sup>125</sup> In a study of young people in the United Kingdom, fewer than 2% reported consistent condom use for oral sex.<sup>126</sup> Various reasons for not using condoms during oral sex have been identified. These include the belief that oral sex feels better without a condom,<sup>50</sup> the dislike of the taste of condoms, and problems negotiating oral condom use with a partner.<sup>126,127</sup>

One recent study did find enough variance in condom use for oral sex to allow for comparisons between those never-using condoms for oral sex (in the past 3 months) and those using condoms at least once for oral sex in that same recall period.<sup>128</sup> The majority of the 353 study participants (82.1%) never used condoms for oral sex while the remaining 17.9% used condoms for oral sex at least once in the 3-month recall period. Those who engaged in relatively higher penile-vaginal sexual frequency, defined as 12 or more sexual acts and measured within the last 3 months, were almost twice as likely to report never use of condoms for oral sex. All of the participants who never used condoms for penile-vaginal sex reported they never used condoms for oral sex. Of interest, the study compared people recruited from a college campus and an STD clinic: those recruited from the college campus were 6 times more likely to report never using condoms for oral sex in the past 3 months. In a study of more than 700 African American adolescent females, nearly one of every 2 adolescents (45.5%) reported they had performed oral sex on a male partner in the past 60 days. Of these, 88.9% ( $n = 288$ ) indicated having one or more episodes of unprotected oral sex (UOS) in that time period thereby meaning that just under 12% did indeed use condoms for oral sex.<sup>129</sup> One likely problem that women may have with condom use during fellatio is the taste and smell of condoms. In a study of nearly 500 heterosexually active men and women from multiple countries, it was observed that 35.4% reported that the smell of condom was a sexual “turn off” and 16.7% reported that the taste was a turn off.<sup>130</sup> Of note, a roughly comparable portion of men indicated that smell was a turn off but less than 8% said this about taste (as might be expected among heterosexual men).

Of course, the bias toward investigating condom use for penile-vaginal sex has also resulted in a dearth of data regarding condom use for anal sex. Anal sex is often regarded as a homosexual behavior occurring between men who have sex with men (MSM) since the majority of research has focused on anal sex as a risk factor for STIs and HIV among this population.<sup>131–135</sup> However, research also indicates anal sex is prevalent among heterosexual



populations,<sup>134–136</sup> including adolescents.<sup>137,138</sup> Anal sex presents a heightened risk for HIV transmission over penile-vaginal or oral sex<sup>139</sup>; thus the promotion of condom use for anal sex among all populations practicing it is crucial to HIV prevention.

Condom use with anal sex is frequently reported to be low and inconsistent across all groups and in a variety of countries.<sup>140–144</sup> A number of cognitive and behavioral issues may account for this. For example, studies report the perception among adolescents that anal sex is not considered sex.<sup>145</sup> There is also evidence from Latin America indicating that women may engage in anal sex as an alternative to penile-vaginal sex in order to preserve their virginity.<sup>146</sup> Both these beliefs may impact how youth translate HIV preventive condom use messages and their use of condoms with anal sex. Additionally, the fact that anal sex does not pose a risk for pregnancy in conjunction with the predominant view of condoms as a contraceptive method may leave some populations ignorant of the necessity of condom use during anal sex for STI and HIV protection.<sup>138</sup> Perhaps due to the HIV preventive focus on condom use for penile-vaginal sex, studies in India<sup>147</sup> and Kenya<sup>148</sup> assessing condom knowledge and use have found that men do not know HIV can be transmitted through anal sex and therefore, tend to not use condoms for anal sex. Other reasons people may not use condoms with anal sex are likely to be similar to those preventing condom use with penile vaginal sex, including fear of erection loss, lack of enjoyment, difficulty in obtaining condoms.<sup>113,149</sup>

## NOVEL INTERVENTIONS TO PROMOTE CONDOM USE

Perhaps the single best success story pertaining to the promotion of condom use comes from Brazil. In the early 1990s the AIDS epidemic in Brazil was not much different than the AIDS epidemic in other hard-hit countries. By the year 2000 AIDS incidence in Brazil had leveled off to about 25,000 cases per year,<sup>150</sup> less than one half the rate reported by the United States for 2006. In the short time between 1996 and 2002 Brazil achieved a 50% reduction in AIDS-related mortality and an 80% decline in AIDS-related hospitalization. Much of this public health success story is a direct consequence of an aggressive Brazilian political effort to promote condom use. Indeed, Brazil's national AIDS program has aggressively pursued the agenda of preventing HIV infection through a web of government programs, including widespread condom promotion campaigns utilizing state-of-the-art social marketing techniques (Fig. 11.1). These efforts exist in stark contrast to the lack of government support (and even opposition) for condom promotion in the United States. Similarly, Brazil has enjoyed great success promoting condom use among CSWs, a population that is blatantly ignored and marginalized in the United States.

In the early years of the AIDS pandemic, Thailand committed to an aggressive campaign designed to raise awareness of HIV/AIDS and to reduce risky behavior. The most well-known component of the program, the 100% Condom Policy, is designed to ensure condoms are used at all times in commercial sex



**Fig. 11.1:** This popular graphic in Brazil let the people know that nothing passes through a condom!

establishments. The policy is accompanied by a mass advertising campaign, by the distribution of free condoms to sex workers, and by a strong collaboration between local authorities, STI clinics, and all sex entertainment establishments.<sup>151–153</sup> Piloted in 1989 and implemented nationally in 1991,<sup>154,155</sup> the program is enormously successful and credited with preventing a 10-fold increase in HIV prevalence in Thailand.<sup>156</sup> The use of condoms with CSWs increased from 14% in 1989 to over 90% in 1992. The annual incidence of STIs nationally rapidly decreased from 400,000 cases per year prior to the campaign to less than 15,000 cases per year since 2000. Finally, the HIV prevalence in at-risk groups such as sex workers, STI patients, and pregnant women has steadily declined since program implementation.<sup>152,157</sup>

The campaign's success is due to a variety of factors, including the foresight and quick response of the Thai government.<sup>158</sup> Since the majority of the sex industry in Thailand and other Asian countries is brothel-based, this setting allows for the creation of a monopoly environment in which condom use is required and noncompliant sex work establishments may be penalized or closed.<sup>153,158,159</sup> Authorities are able to monitor condom use to some degree by tracking new STIs through an extensive network of STI clinics, routine examinations among sex workers, monitoring the number of condoms provided to sex work establishments, and by sending volunteers to test compliance.<sup>158,159</sup> Success is also due to penalizing noncompliant sex business owners, pimps, and customers rather than sex workers and to the fact that the policy bypasses economic and power differentials between sex workers and clients which can decrease effectiveness of STI/HIV prevention strategies relying on condom negotiation skills alone.<sup>153</sup> With guidance from the WHO,<sup>160</sup> variations of Thailand's 100% condom campaign have been instituted elsewhere in Asia, including Cambodia, Philippines, Vietnam, China, Myanmar, Mongolia, and Laos.<sup>152</sup>

Of note, a similar effort occurred recently in China, where a 100% condom use program (again, aimed at commercial workers) increased rates of condom use from 60% to 95% 12 months later, with corresponding decline in rates of chlamydia.<sup>161</sup>

In sub-Saharan Africa and in Asia, a systematic review of behavioral-based STI and HIV interventions suggests that the majority of preventive efforts directed at condom use are with partners in commercial sex or casual sex relationships. Further, substantial evidence indicates that the greatest increases in condom use have been achieved in these relationship contexts while interventions targeting youth or the general population were less successful or did not report significant changes in condom use.<sup>162</sup> One of the more successful youth-targeted interventions was delivered in Namibia; it offered training in communication and decision-making skills as supplement to HIV/AIDS education. As a result, youths participating in the intervention felt more capable of asking for condoms in clinics and of maintaining intimate relationships without having sex.<sup>163</sup> Overall, the most effective condom-use interventions reported using peer or other forms of health education, condom provision, and STI testing and treatment, suggesting that these three components may be very effective in combination. The review's findings are consistent across both sub-Saharan Africa and Asia.<sup>162</sup>

Other intervention attempts at increasing condom use take a structural approach intended to operate within economic, gender, and power frameworks in a society. For example, in South Africa, where 5.7 million people are living with HIV, the lack of development and economic opportunities in addition to persistent gender inequalities create an environment conducive to HIV risk. Structural interventions, such as the Intervention with Microfinance for AIDS and Gender Equity (IMAGE), work to positively change the social context and thereby influence multiple risk behaviors and health outcomes. IMAGE combines microfinance, a development tool that provides loans to people for income generation, with gender equity training and HIV education. During microfinance meetings, loan recipients participate in a 12–15 month training which addresses gender roles, cultural beliefs, relationships, communication skills, intimate partner violence (IPV), and HIV risks. The training further provides leadership opportunities for participants to mobilize their communities against issues such as IPV and HIV. Although the IMAGE intervention demonstrated increases in household economic well-being and women's empowerment and decreases in IPV, changes in sexual behavior, condom use, and HIV incidence were limited.<sup>164</sup> Long-term effects remain to be seen, but the integration of condom promotion into broader, structural-level programs is likely to continue in future prevention efforts.

Of course, government led and supported efforts to promote condom use represent a mere fantasy for STI prevention professionals in a vast number of countries. Thus, community-based and clinic-based programs have been tested for efficacy. Perhaps one of the best known and novel community-based approaches involves the use of popular opinion leaders.<sup>165</sup> In typical studies that use the popular opinion leader (POL) model, trained prevention specialists will identify key opinion leaders in a given community of persons being targeted for increased use of condoms. After being provided with extensive training, the selected opinion leaders begin to diffuse their condom

promotion messages to others in the community via face-to-face interactions. The model has been widely applied across different at-risk populations and in multiple countries.<sup>166</sup> Perhaps one of the best examples was reported by Kelly and colleagues.<sup>167</sup> In 1997 Kelly and colleagues published findings from the trial of a POL model applied in gay bars. Men attending gay bars in 8 cities were assessed as a barometer of program effectiveness. Compared to baseline assessments, the assessments made at the 1-year follow-up indicated a significant decline in unprotected anal intercourse (UAI) in the 4 cities that received the intervention program (from a baseline mean of 1.68 acts in the past 2 months to a 1-year mean of 0.59 acts,  $p = 0.04$ ).

An example of a novel, clinic-based, condom use promotion program is known as Focus on the Future.<sup>168</sup> This extremely brief program was predicated, in part, on the principle that effective behavioral intervention is contingent upon the careful development of culturally tailored approaches. The approach was based on five categories of condom-related issues identified from qualitative studies. These categories pertained to: (i) the “fit and feel” of condoms; (ii) condom brand and size; (iii) application problems; (iv) availability of condoms and lubricants; and (v) commitment to condom use. Collectively, these points suggested that men may use condoms more often if they could learn how to use them without feeling that they compromise the overall sexual experience. Thus, the unstated intent of the program was to “sexualize” condoms so that men would find them to be compatible with their goal of enjoying sex. A key part of this strategy was to provide men with a wide variety of condoms (including specialty condoms that are normally too expensive for many men to purchase) and to provide men with small plastic packages of water-based lubrication for condoms (in multiple flavors, scents, and colors). Much of the brief teaching session (conducted using a one-to-one format by a lay health advisor) was devoted to letting men learn about condom brands and sizes, letting them practice condom application of penile models, and giving them instruction on the value and use of lubricants. Compared to men randomized to a control condition, those receiving the intervention were significantly more likely to report using condoms at last sex episode (72.4% vs. 53.9%,  $p = 0.008$ ) and they reported fewer acts of unprotected sex (mean of 12.3 vs. 29.4,  $p = 0.045$ ).<sup>168</sup> This type of program (brief and clinic-based) may have a great deal of utility as it can easily be incorporated into the everyday practice of STD clinics. For skeptics arguing that implementation of even brief clinic-based condom promotion program require hiring a staff member (i.e., a health educator), it is worth noting that a recent pilot study has found promising results from a self-guided home-based intervention program designed for young men.<sup>169</sup> A central aspect of this intervention approach was to provide young men with a “prescription” for individual practice, designed to enhance condom use skills, comfort, and confidence in a situation where the performance pressure inherent in partnered sex should be attenuated. In this self-guided intervention, young men were provided with brief instructions on condom use and the opportunity to use a variety of condoms and lubricants to

allow them to discover the optimal products for their needs. The research team found significant increases in participants' sexual sensation during condom use, their reported levels of comfort using condoms, and their self-efficacy for condom use. Further, they found significant reductions in reported problems with the "fit and feel" of condoms, a variable that has been a fairly robust predictor of condom breakage.<sup>111,113,114</sup> Significant increases were also observed relative to adding water-based lubricants to condoms and a significant decrease in condom-associated erection loss was observed.

## Condoms and Politics

Promoting the use of condoms for STI and HIV prevention is futile if condoms are not readily available. Indeed, the lack of access to condoms still remains a significant barrier to STI/HIV prevention today. In most countries, condom availability results from a combination of government, private sector, and nonprofit efforts; these efforts are frequently supported by the United Nations Population Fund (UNFPA; the United Nations agency responsible for providing condoms) which integrates the provision of condoms as a component in its broader HIV prevention program. Despite these combined efforts, data from the UNFPA suggest that condom shortages frequently occur. In 2004, the provision of 2.1 billion condoms by bilateral donors, the UNFPA, and social marketing organizations to sub-Saharan Africa only stretched to about 10 condoms per man of reproductive age.<sup>68</sup> Earlier research found that sub-Saharan African countries providing the most condoms still averaged only about 17 condoms per man; 1.9 billion more condoms would be needed in order to replicate that level of provision for other sub-Saharan African nations.<sup>170</sup> The shortage of condoms often creates inefficiencies in other aspects of STI/HIV prevention. For example, an evaluation of condom distribution in Sao Paulo, Brazil, found that regular condom shortages influenced the management of available condom resources. Distribution became based on "first-come, first-serve" basis, such that condoms were not distributed with any epidemiologic impact and were not distributed actively.<sup>171</sup> Finally, in many resource-poor nations, condoms often come at the cost of other national needs; the purchase of condoms not covered by donations may take government funds from food, medicine, and other necessities.<sup>68</sup>

Even when condoms are available, there are a number of factors which may affect their accessibility. Condoms are often provided for free in public clinics; however, there is evidence that condoms offered for free are viewed as old or of inferior quality.<sup>172</sup> Regularly purchasing condoms available in the commercial sector may prove expensive for some people although research among adolescents in urban Cameroon determined that free and commercial distribution programs can effectively complement each other. In this study, sexually inexperienced youth were more likely to be reached by free condom programs while sexually experienced youth showed higher rates of condom use and fewer wasted condoms with condoms purchased from commercial programs.<sup>173</sup> Additionally, condoms provided freely by government or donor

agencies may not represent the variety in size, fit, and style represented in the commercial sector. A randomized controlled trial among men in Jamaica testing the impacts of variety in condom choice found that choice increased men's perceived sexual pleasure with condoms but did not impact their level of condom use or STI incidence.<sup>174</sup> In contrast, qualitative research conducted among African American men in the southern United States emphasized that men experienced problems with the "fit and feel" of free condoms available at clinics.<sup>112</sup> Clearly, condoms of appropriate size, fit, and monetary cost are not always readily accessible.

Additionally, there are other costs associated with condom accessibility; for example, in some areas in South Africa, access to condoms involves substantial travel time and travel costs to distribution sites.<sup>175</sup> Research investigating access to condoms in rural Tanzania found people usually had to walk 3–10 kilometers before reaching the government health facilities distributing condoms.<sup>172</sup> Researcher attempts to access condoms from public health clinics in Kwa-Zulu Natal, a region in South Africa with a concentrated HIV/AIDS epidemic, found that although clinics were accessible by walking, nearly all were poor or inadequately signed. Furthermore, the clinic hours of operation were limited to business hours during the weekdays, and some clinics restricted the hours in which condoms were distributed.<sup>176</sup> Such barriers may have particular impact on at-risk populations such as adolescents who are in school during clinic or condom distribution hours.<sup>176,177</sup> Evidence from Zambia also suggests that condom access may differ across sociodemographic characteristics as well. Study findings suggested that poorer men had greater access to condom outlets within their neighborhood while wealthier men had fewer opportunities to access condoms nearby.<sup>178</sup>

Further costs in accessing condoms may include the social stigma, embarrassment, and judgmental or hostile attitudes of providers. Qualitative work in the United Kingdom suggests that embarrassment and fear of judgment is a key barrier to adolescents accessing condoms, STI/HIV information, and sexual health advice.<sup>179</sup> Both condom providers and customers in Tanzania reported embarrassment in interactions regarding the exchange of condoms or questions about condoms. Customers also believed that health workers and condom distributors would not keep such exchanges confidential or private.<sup>172</sup> The lack of a private space in which to purchase or gain instruction in the application of condoms has also been reported as a barrier to accessibility elsewhere.<sup>176,179</sup> These studies in settings as diverse as the UK and Tanzania suggest that the need for privacy and anonymity is heightened in rural areas where populations are small and the disapproving scrutiny or gossip from others may be overwhelming.<sup>172–179</sup>

There is also a gender component to condom accessibility which may serve as barriers to both sexes. Family planning clinics, for example, generally target female clientele and this has frequently fueled the perception that services, including the provision of condoms, are not available for men. The female focused environment at family planning clinics can also deter



men from feeling comfortable enough to seek condoms at these locations.<sup>180</sup> Conversely, social attitudes may make condom provision to males more acceptable than to females. A South African study found male research staff attempting to access condoms at a variety of locations received more attention and information than their female counterpart. Male research staff members were provided with more demonstrations in how to use condoms while female research staff recorded instances in which condom providers refused to provide condom use instructions or condom-related consultation with a physician.<sup>176</sup>

The attitudes and opinions of various parties as well as the political climate may influence condom availability and accessibility in a region. The provision of condoms to adolescents is one such example since this issue generally creates social division wherever considered. Many people believe the availability of condoms to adolescents endorses adolescent sexual behavior and causes increases in adolescent sexual activity<sup>181–183</sup> although empirical research has proven otherwise.<sup>184–186</sup> Others cite moral concerns in their argument against condom promotion, stating that it will undermine the preservation of traditional values such as abstinence until marriage.<sup>177</sup> Proponents of condom provision for adolescents may argue that adolescent sexual activity is inevitable and youth should be provided with means to protect themselves from infection.<sup>185</sup> The mix of these opinions and their impact on health policy in an area can heavily impact the availability of condoms for youth.

## Female Condoms

In 1993, the United States Food and Drug Administration (FDA) approved the first version of the female condom (FC1) as a barrier contraceptive providing limited protection against STIs. FC1 consists of a lubricated polyurethane sheath with two flexible rings (one attached and one unattached). Similar to a diaphragm the ring at the closed end of the device is inserted into the vagina (protecting the cervix), while the ring at the open end remains outside the vagina partially covering the labia. The FDA approved a second version of the female condom (FC2) for US marketing in March 2009. This new version is made of nitrile, a material less expensive than polyurethane.

The United States Centers for Disease Control (CDC) and the FDA continue to recommend the use of female condoms as an effective alternative mechanical barrier to viruses when male condoms cannot be used. This conditional recommendation reflects that while laboratory studies indicate that the female condom provides protection from STI pathogens,<sup>187</sup> only a limited number of applied studies have assessed the effectiveness of female condoms in preventing STIs.<sup>188–191</sup> While continued research in this area is necessary and continues to be encouraged by the CDC, the WHO, United States Agency for International Development (USAID), and other global health organizations, it is important to focus on the fact that female condoms are an alternative barrier method that confer similar protective values as male condoms when

used consistently and correctly and under some circumstances female condoms may be the only option for protection for women at risk of contracting HIV.

Female condoms allow women more control over the use of a barrier method contraceptive. This advantage is particularly important as a means of protection against STIs, including HIV for women in situations where their male partners refuse or are reluctant to use male condoms. Numerous socioeconomic, cultural, and historic factors promote a global environment where women are particularly at risk for contracting STIs, including HIV.<sup>192</sup> Around the world women are increasingly at risk for HIV/STIs through heterosexual contact.<sup>193,194</sup> Thus, for many women female condoms provide an opportunity for self-protection under circumstances of limited power. Additional benefits of the female condom include: (i) individuals allergic to latex can use them; (ii) both water based and oil based lubricants can be used; (iii) they do not require a prescription or fitting; and (iv) they do not require a penile erection (Planned Parenthood).

While female condoms have many advantages, some prominent disadvantages of this method should be noted. Cost is one of the most obvious disadvantages and barriers to use. This problem led to investigations on whether the FC1 device could be used multiple times. In 2002, the WHO issued a statement on reuse of FC1, which did not recommend reuse of the device but provided a draft protocol for handling and preparation for reuse.<sup>195</sup> This decision was based on the complex contextual factors that at times make weighing the risks and benefits of reusing FC1 a decision to be made locally. The FC2 is 30% less expensive than the FC1, but these new female condoms are still 15–20 times more expensive than male latex condoms and approved for one time use only.<sup>196</sup>

Other disadvantages of female condoms include the following: (i) some individuals experience irritation of the vagina, vulva, or penis; (ii) slippage of the device into the vagina may occur; (iii) unpleasant or distracting noises have been reported with use of FC1; and (iv) similar to male condoms individuals report reduced feelings during intercourse.<sup>197</sup> Additionally, female condoms are detectable by male partners, and negotiating their use with partners already opposed to male condom use and suspicious of female infidelity may be difficult for women.<sup>198</sup>

There is a dearth of studies assessing the direct effectiveness of female condoms in the prevention of STIs. A larger body of research has focused on general awareness and use of female condoms.

An important question for health researchers working in HIV and STI prevention is whether female condoms are actually being accepted and used by women and their sex partners around the globe. Studies examining the general acceptability and use of female condoms suggest that general use remains limited. One study examining HIV prevention strategies other than male condoms among low-income heterosexually active women found that 16% of the 1469 women expressing an HIV/STI prevention method preferred the female condom.<sup>199</sup>

In another study, examining female awareness and use among female Nigerian college students, researchers found 11.3% of



850 women had ever used the female condom.<sup>200</sup> These female condom users reported using the female condom to: (i) prevent unwanted pregnancy and STIs including AIDS (40%); (ii) to prevent pregnancy only (27.1%); and (iii) to prevent STIs including HIV only (19.8%). Interestingly, almost half (47%) of the women using female condoms reported their sex partners approved of using it.

Studies have also investigated potential markers of female condom use. Similar to male condom use, partner type tends to play a role in the use of female condoms. For example, a study of inner city African American women ( $n = 280$ ) found women with multiple sexual partners were 5 times more likely to use female condoms than women in a monogamous relationship.<sup>201</sup> Furthermore, a study conducted after a social marketing campaign in Zimbabwe ( $n = 1740$ ) found variables associated with consistent use among males and females differed between individuals with marital and nonmarital partners.<sup>202</sup> Variables associated with consistent use among individuals with marital partners suggests female condoms are used for pregnancy prevention alone, while variables associated with consistent use with nonmarital partners suggests female condoms are used for both pregnancy and STI prevention.

While general use of female condoms remains limited, behavioral interventions promoting use and acceptability of the device suggest that under some circumstances female condoms remain at the very least an additional option for STI, including HIV protection for some women. This has been particularly true for those women most at risk for contracting STIs.<sup>203–207</sup> These early interventions were delivered to a wide range of samples and utilized various prevention activities to promote behavior change.

Findings from more recent randomized control trials suggest female condoms may still be a viable option for protection, and behavioral interventions can increase use and acceptability. For example, a small-group skills training intervention delivered to women with risk factors (e.g., a diagnosed STI, multiple sex partners, IDU, or a high risk sex partner) found at the 3-month follow-up that 59.9% of intervention participants compared to 21.9% of control group participants used the female condom at least once.<sup>208</sup> Another study compared an 8-session and 4-session group counseling intervention to an assessment only control and found first-time female condom use was increased in the 8-session intervention compared to the 4-session intervention, and in the 4-session intervention compared to the control group.<sup>209</sup> In yet another randomized trial that compared participants in a female condom skills training to those in a general health promotion group, results indicated that at both the 3-month and 6-month follow-up participants in the intervention were more likely to have used the female condom than those in the control group.<sup>210</sup>

Most interventions have focused on female participants alone; however, a recent intervention focused on heterosexual couples. Couples were assigned to one of three conditions: (i) a 6-session relationship-based intervention for the couples together; (ii) the

same intervention delivered to women alone; or (iii) a women's only control group receiving a one-time education session.<sup>211</sup> While there were no significant differences in female condom use between the two intervention groups at the 90-day follow-up, participants in both intervention groups were more likely to have used a female condom than control group participants. Intervention participants also reported being more likely to intend to use female condoms in the next 90 days than the control group.

These recent studies, as well as earlier literature suggest behavioral interventions can, in fact, increase use of female condoms, at least in the short term. These studies also highlight some other interesting points about promoting female condom use. First, interventions should include counseling on both information and skills based training (including self-insertion practice).<sup>208–210</sup> Second, those promoting female condom use may want to continue exploring couples-based interventions.<sup>211</sup> Finally, interventions promoting female condom use do not necessarily decrease male condom use.<sup>210</sup> Promoting female condom use can create an environment where mixing the use of female and male condoms ultimately leads to more consistent condom use for women most at risk of contracting STIs, including HIV.<sup>203,206</sup>

## Other Barrier Methods—Diaphragms and Cervical Caps

Diaphragms are a female controlled contraceptive method that can be used in many circumstances without a male partner's detection. The device is a latex cup inserted into the vagina prior to sexual intercourse, and it requires an examination and a prescription. As a contraceptive device, it is traditionally used in conjunction with spermicide. A recent study comparing contraceptive efficacy between use of the diaphragm alone and with spermicide was unable to confirm efficacy of the diaphragm alone.<sup>212</sup> This is somewhat troubling considering the use of spermicide is discouraged for women at risk for STIs including HIV. With this said, researchers concerned with the lack of choices women have to protect themselves from increasing rates of heterosexual HIV transmission are proposing the diaphragm as an alternative method of HIV protection.<sup>213,214</sup>

The diaphragm is a device that protects the cervix, and limited observational studies offer some evidence that the diaphragm offers protection from STI pathogens including gonorrhea.<sup>214</sup> As studies are underway investigating the actual efficacy of the device, other researchers have begun the process of exploring the acceptability of diaphragms.<sup>215–217</sup> These acceptability studies suggest barriers to use exist, but some women will be open to using the diaphragm as an additional means of protection if and when its efficacy as a form of HIV prevention is clear.

Similar to the diaphragm, cervical caps are another female controlled barrier contraceptive. Instead of latex, cervical caps are made of silicone and they too require an examination and prescription. Like the diaphragm women can insert cervical caps prior to sexual intercourse and a male partner unwilling to use protection from STIs can often not detect them.<sup>218</sup>

Clearly additional research is needed to confirm the STI protective value of barrier devices such as the diaphragm and cervical caps, but early research suggests if and when their protective value is confirmed these devices can be another option for protection for women most at risk for STIs including HIV. Additional studies will also need to consider how diaphragms and cervical caps can be combined with vaginal microbicides to offer women increased protection.

## Vaginal Microbicides

Globally, perhaps the greatest single hope for a reduction in AIDS rests on the premise that women (and perhaps willing male partners) will insert chemical products into the vagina before sex occurs in order to destroy HIV if it is present in the ejaculate. Like all biochemical innovations, the successful use of vaginal microbicides will require behavioral intervention (i.e., education, skill acquisition, and access to the product). Unfortunately, only a few behavioral studies have focused on men. This is attributable to the original intent of microbicide development, i.e., to provide women with a clandestine method for preventing HIV. However, as microbicide research advances it has become clear that women may indeed want and even need to include their male sex partners in the use of microbicides.<sup>219,220</sup>

Although studies of women suggest that enhanced intimacy and trust are primary motivations for involving men, it should also be recognized that mutual action may aid in the correct use of microbicides. Just as condoms are frequently used incorrectly, great potential for user error also exists with microbicides. Recent evidence suggests that condom use errors and problems are reduced when condom use is a mutual decision<sup>120</sup> and this same phenomenon may apply to microbicides. Moreover, studies of men suggest that they may indeed be supportive of couple-based decisions regarding microbicide use as long as sexual pleasure is not compromised.<sup>221,222</sup> A primary concern of men appears to be the excessive “wetness” that will inevitably occur with application of the 3.5 ml of gel. As described in one research article, microbicides might become widely used if they do not substantially lubricate the vagina.<sup>221</sup> This point is critical because it is now clear that the likely carrier for a successful microbicide will be a gel and therefore “substantial lubrication” of the vagina is inevitable. Moreover, the scientific community is well aware that poorly lubricated vaginal tissue is far more susceptible to abrasion thereby magnifying risk of HIV transfer. Thus, one important behavioral question that must be immediately addressed is, “How can men be motivated to consistently accept the presence of a gel added to the vagina during heterosexual intercourse?”

A second question is equally important: “Will men replace condom use by use of microbicides?” This question has not been studied extensively; however, several mathematical modeling analyses have suggested that extensive condom replacement would need to occur before the overall public health benefit of a relatively effective microbicide would be negated.<sup>223,224</sup> The mathematical modeling exercises are flawed, unfortunately, in that they do not consider the prevalence and effect of common STDs (e.g., chancroid, syphilis,

chlamydia, genital herpes, trichomoniasis, and HPV) on either microbicide efficacy or susceptibility to HIV acquisition. Indeed, current evidence suggest that a “healthy vagina” (i.e., disease free, including lack of bacterial vaginosis) is a prerequisite to optimal microbicide effectiveness.<sup>225</sup> Rates of condom replacement may also vary widely by age, with young men potentially being more likely to forgo condoms given the introduction of microbicides. It is now widely apparent that the first generation of microbicides will need to be introduced in conjunction with efforts to promote and sustain condom use.<sup>226</sup> In essence, this simple observation necessitates male partner involvement and requires the application of efficacious (but brief) teaching protocols shown to promote men’s consistent and correct use of condoms.

### Summary

Barrier methods of STI prevention are vital tools for controlling the spread of epidemics worldwide. In particular, condom use is the primary method of prevention. Given adequate attention to the promotion of both the consistent and the correct use of condoms, this method can greatly mitigate the spread of STIs. Ongoing behavioral research regarding how best to achieve this promotion is needed across all at-risk populations. Like so many other aspects of public health, the promotion of condoms will be greatly facilitated by the support of local governments; doing so is vital to STI prevention. The use of female condoms, cervical caps, and diaphragms also represents a valuable set of prevention methods, with each having unique advantages and with each involving challenges that can be met through creative promotion approaches. Finally, the prospect for future approval and use of vaginal microbicides warrants immediate behavioral research.

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# Prevention of HIV and other Sexually Transmitted Infections: Male Circumcision

# 12

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## Introduction

Three randomized controlled trials (RCTs) in sub-Saharan Africa have shown that circumcised men are at reduced risk of HIV infection. In this chapter we review the evidence that male circumcision reduces risk of HIV and other sexually transmitted infections (STIs), and discuss current research and public health implications of the findings for HIV transmission.

## Background

Male circumcision is the surgical removal of the prepuce, or foreskin, of the penis. It is one of the oldest and most common surgical procedures performed worldwide, with approximately 30–35% of men circumcised worldwide.<sup>1</sup> Circumcision is practiced for religious, social, and medical reasons. Overall, approximately two-thirds of circumcised men are Muslim, with coverage almost universal in the Middle East, North Africa, Pakistan, Bangladesh, and Indonesia. Circumcision is also practiced for nonreligious reasons either neonatally or as a rite-of-passage to manhood and is very common in West Africa, parts of Central and Eastern Africa, the United States, Republic of Korea, and the Philippines.<sup>1</sup> Within countries, prevalence can vary widely with religion, ethnicity, and socioeconomic status. For example, in Kenya, circumcision is almost universal in most ethnic groups, but has traditionally been uncommon among the Luo, who reside mainly in western Kenya.

The age at which circumcision is undertaken is determined by sociocultural and religious traditions, and it may occur from the neonatal period to early adulthood. Cultural attitudes toward circumcision can change over time, and there have been rapid increases and decreases of prevalence in several settings among non-Muslims and non-Jews, which may result from increased mixing between different cultures, religions, and socioeconomic groups, or from changes in perceptions of health or sexual benefits associated with the practice.<sup>1</sup>

## Biological Evidence for a Protective Effect of Circumcision on HIV/STIs

There are several mechanisms by which the presence of the foreskin may increase a man's risk of acquiring STIs, including HIV. The warm, moist environment under the foreskin favors pathogen survival and replication, as shown by recent data from Uganda where, following circumcision, men had fewer proinflammatory anaerobic bacteria.<sup>2</sup> These bacteria may exacerbate existing infection and increase risk of genital ulcer disease (GUD) in uncircumcised men. Further, unlike the glans penis and the outer surface of the foreskin, the inner mucosal surface of the foreskin is thinly keratinized<sup>3</sup> and hence susceptible to minor trauma and abrasions which facilitate entry of pathogens.<sup>4</sup> Finally, lesions and ulcers produced by STIs may be less well-detected and treated in uncircumcised men.

An increased risk of GUD in uncircumcised men provides a potential pathway for increased risk of HIV, through the disrupted mucosal surface. In addition, the foreskin is likely to increase the risk of HIV infection specifically as tissue from the inner surface of the foreskin mucosa contains higher proportions of HIV-1 target cells than cervical tissue.<sup>5</sup> Further, the HIV-1 target cells in the inner foreskin are closer to the epithelial surface than those situated elsewhere in the penis, due to the lack of keratin,<sup>3</sup> and are more easily infected during exposure to vaginal secretions. In contrast, in circumcised men, the penile shaft is thought to be covered with a thickly keratinized epithelium, providing some protection from infection.<sup>3</sup>

## Epidemiological Evidence for a Protective Effect of Circumcision on HIV/STIs

### ASSOCIATION BETWEEN MALE CIRCUMCISION AND RISK OF HIV INFECTION IN HETEROSEXUAL MEN

The hypothesis that male circumcision might protect against HIV infection was first suggested in 1986<sup>6,7</sup> and was subsequently supported by ecological studies showing correlation between areas



of low prevalence of male circumcision and high HIV prevalence in sub-Saharan Africa in the late 1980s,<sup>8,9</sup> and, later, across 118 developing countries.<sup>10</sup>

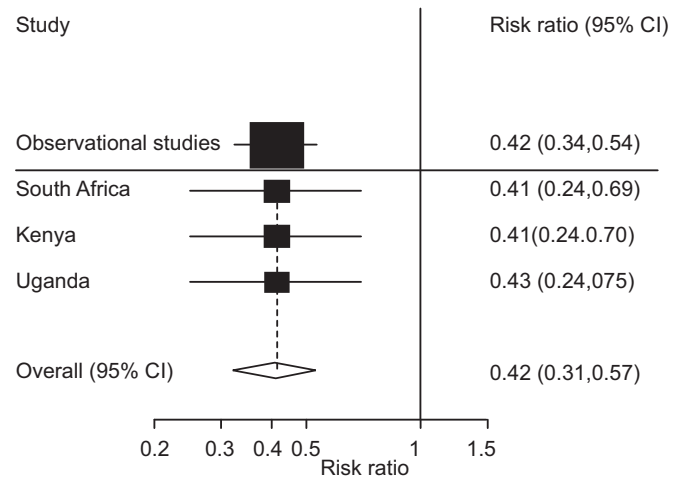
A systematic review and meta-analysis of 27 studies from sub-Saharan Africa was published in 2000,<sup>11</sup> showing that circumcised men were at significantly lower risk of HIV infection after adjusting for potential confounding factors (adjusted risk ratio [RR]=0.42, 95% confidence interval [95% CI] 0.34–0.54). A subsequent systematic review published in 2005 confirmed these findings.<sup>12</sup> However, observational epidemiological studies are inherently limited by potential biases and cannot provide conclusive evidence that circumcision reduces risk of HIV infection. Researchers therefore initiated three RCTs of circumcision among adult men in 2002–2003, to investigate the potential association more rigorously.

These trials recruited men willing to be circumcised in traditionally noncircumcising communities in Uganda, Kenya, and South Africa. In total 10,908 men were randomized to be offered immediate circumcision (intervention arm) or circumcision at the end of the trial (control arm), and were followed-up for up to 2 years to compare HIV incidence in the two arms. Trial characteristics are shown in Table 12.1.<sup>13–15</sup> In all 3 trials, an independent Data and Safety Monitoring Board recommended the trial be stopped early as higher HIV incidence was seen among men randomized to the control arm. Overall, men randomized to the circumcision arm were at approximately 60% less risk of becoming HIV infected during the trial than men in the control arm, a finding consistent with that observed in the observational studies (Fig. 12.1).<sup>16,17</sup>

Following publication of the trial results in early 2007, the World Health Organization and the Joint United Nations Programme for HIV/AIDS organized an international consultation of researchers and stakeholders to discuss the implications of these findings. The participants concluded that there was compelling evidence that male circumcision partially reduced the risk of HIV acquisition, and that promotion of male circumcision should be included as an additional HIV strategy for the prevention of heterosexually acquired HIV infection in men.<sup>18</sup>

**Table 12.1:** Summary of Three Randomized Controlled Trials of Male Circumcision on HIV Acquisition in Sub-Saharan Africa

	South Africa	Uganda	Kenya
Trial setting	Semi-urban	Rural	Urban
Background HIV incidence	~3–5/100 person years	~1.5/100 person years	~2.5/100 person years
Age range	18–24	15–49	18–24
Surgeons	General MDs	Medical officer	Medical officer
Surgical method	Forceps guided	Sleeve	Forceps guided
Number of men (final)	3520	5000	2800



Taken from (Weiss, Halperin et al. 2008)<sup>16</sup>

**Fig. 12.1:** Random-effects meta-analysis for the randomized controlled trials with summary risk ratio for the observational data.

## ASSOCIATION BETWEEN MALE CIRCUMCISION AND RISK OF HIV INFECTION IN HETEROSEXUAL WOMEN

A fourth RCT was conducted in Rakai, Uganda, to evaluate the impact of male circumcision on HIV acquisition in women. In this trial, 922 HIV-infected men were randomized to either immediate or delayed circumcision.<sup>19</sup> The men were aged 15–49 years old, asymptomatic, and with CD4 counts of 350 cells/ $\mu$ L or more. A total of 163 uninfected female partners were enrolled at the same time as the men, and followed for up to 24 months. However, the trial was stopped early due to the small number of female partners enrolled at the same time as the men. Over the 24 month follow-up period, 22% of the females in the intervention arm seroconverted compared with 13% in the control arm (hazard ratio=1.58, 95% CI 0.68–3.66). This study therefore provides no evidence that circumcision protects against male-to-female HIV transmission. Further, there was some evidence that recently circumcised HIV-positive men who resumed sexual activity early may be more likely to transmit HIV in the first 6 months after surgery than those who wait until complete wound healing, but these numbers are too small to be conclusive. Among the 18 couples in the intervention arm who resumed sex more than 5 days before certified wound healing, there were 5 seroconversions (27.8%), compared with 6/63 seroconversions (9.5%) among those who first had sex after this time ( $p=0.06$ ). This latter figure is similar to the seroconversion risk among couples in the control arm (6/68; 8.8%).<sup>19</sup>

Although there may be no direct impact of circumcision on male-to-female transmission, there will be an indirect benefit to women if expanded circumcision services reduce HIV prevalence in their male partners. Mathematical modeling shows that these benefits will likely take several years to become evident, and

will increase over time, with subsequent reductions in rates of mother-to-child transmission.<sup>20</sup>

### ASSOCIATION BETWEEN MALE CIRCUMCISION AND RISK OF HIV INFECTION IN MEN WHO HAVE SEX WITH MEN

The implications of the trial findings for men who have sex with men (MSM) are unclear. HIV transmission from penile-anal intercourse is predominantly to the receptive partner<sup>21</sup> a risk unlikely to be directly modified by his circumcision status. However, it is biologically plausible that male circumcision provides partial protection against HIV acquired through insertive anal intercourse, as it does for vaginal-penile intercourse. There have been no RCTs of circumcision among MSM, but a meta-analysis of 18 observational studies conducted worldwide found little association of male circumcision with HIV infection (OR=1.02, 95% CI 0.83–1.26).<sup>22,23</sup> The message for all men, regardless of sexual orientation or circumcision status, is that practicing safer sex behaviors, including correct and consistent condom use, is the best way to avoid infection.

### ASSOCIATION BETWEEN MALE CIRCUMCISION AND RISK OF OTHER SEXUALLY TRANSMITTED INFECTIONS

The RCTs also provide data on the association between circumcision and STIs (Table 12.2). In general, the associations seen are weaker and less consistent than the findings for the association with HIV infection. The trials from Uganda and South Africa indicate that men in the circumcision arm had around 30% less risk of acquiring HSV-2 (adjusted hazard ratio (HR) 0.72, 95% CI 0.56–0.92 in Uganda and 0.68, 95% CI 0.38–1.22 in South Africa).<sup>24–26</sup> The Ugandan trial has reported no impact on serological syphilis, (adjusted hazard ratio 1.14, 95% CI 0.77–1.75), but significant reduction in the incidence of HSV-2 and HPV infection<sup>26</sup>. The risk of self-reported GUD was significantly lower among circumcised men in the Kenyan trial (RR = 0.53), and among both HIV positive and HIV negative

men in the Ugandan trials (RR = 0.63, 95% CI 0.5–0.8 and 0.54, 95% CI 0.46–0.66, respectively).<sup>27,28</sup>

The trials have also provided data on the association of circumcision with nonulcerative STIs (Table 12.2). The strongest effect of circumcision was observed on *Trichomonas vaginalis* prevalence in the South African trial, where circumcised men were less likely to be infected at the final follow-up visit compared to uncircumcised men (adjusted odds ratio 0.47, 95% CI 0.25, 0.92),<sup>25</sup> although a weaker effect on *Trichomonas vaginalis* incidence was seen in the Kenyan trial.<sup>29</sup> A reduced risk of *Trichomonas vaginalis* in female partners of circumcised men was also seen in the Ugandan trials of both HIV positive and negative men, as well as a reduced risk of bacterial vaginosis in female partners of HIV negative, but not positive, men.<sup>19,30</sup> There is relatively little evidence of an effect of circumcision on *Chlamydia trachomatis* in the trials,<sup>25,29</sup> and no impact on *Neisseria gonorrhoeae*.<sup>25,29</sup>

Finally, a strong effect of circumcision was also observed on the prevalence of human papillomavirus (HPV) at the final follow-up visit in both the Ugandan and South African trials.<sup>26,31</sup> In both trials the prevalence of high-risk HPV (HR-HPV) isotypes was approximately 30–35% lower in the circumcised arm compared to control arm. A meta-analysis of observational studies also found that circumcised men were at significantly lower risk of HPV (OR=0.52, 95% CI 0.33–0.82).<sup>32</sup> A lower risk of HPV prevalence among circumcised men could indicate that circumcision decreases either HPV incidence, or increases clearance rates, and further work is needed to elucidate these findings. A randomized trial found reduced prevalence and incidence of high risk HPV in the female partners of circumcised men,<sup>33</sup> and by implication lower risks of cervical and penile cancers.

The Ugandan trial reported greater efficacy on HIV among men at higher risk (those with nonmarital sexual partners, reporting transactional sex or having a history of genital ulcers); i.e., about 75% risk reduction. A similar observation was seen in the earlier meta-analysis of observational data (adjusted RR=0.29, CI 0.20–0.41). A stronger protective effect in high risk groups may be due in part to circumcision protecting against other STIs, thus providing additional indirect protection against HIV. However, models indicate that a relatively small proportion of the impact of circumcision on HIV is mediated through GUD or other STIs. Models based on the Kisumu data estimate that about 10–20% of the HIV infections prevented by male circumcision were due to efficacy against STIs.<sup>34</sup>

**Table 12.2:** Impact of Male Circumcision on STIs in Men

STI	Outcome measure	Trial	RR	95% CI
HSV-2	Incidence	South Africa	0.66	0.39–1.12
		Uganda	0.72	0.56–0.92
<i>N. gonorrhoeae</i>	Prevalence	South Africa	0.94	0.69–1.29
	Incidence	Kenya	0.95	0.68–1.28
<i>Chlamydia trachomatis</i>	Prevalence	South Africa	0.56	0.32–1.00
	Incidence	Kenya	0.87	0.65–1.16
<i>Trichomonas vaginalis</i>	Prevalence	South Africa	0.53	0.28–1.02
	Incidence	Kenya	0.77	0.44–1.36
HPV	Prevalence	South Africa	0.66	0.51–0.86
		Uganda	0.65	0.46–0.90
Syphilis	Prevalence	Uganda	1.14	0.77–1.75

### Scale-up of Male Circumcision for HIV Prevention

Following the recommendations by WHO/UNAIDS in 2007,<sup>18</sup> several countries in southern and eastern Africa are introducing or expanding safe male circumcision programs, with funding from international donors. These include operational research studies to monitor key programmatic issues including the safety

of the procedure, counseling to minimize risk compensation (i.e., increased unprotected sex among circumcised men who feel they have an “invisible condom”), impact on sexual function and satisfaction, and methods to match supply and demand of circumcision. For example, studies on the impact of circumcision on sexual function have been conducted in the trial settings, and in Uganda very high levels of satisfaction (>98%) were reported in both arms of the trial and in Kenya reported sexual dysfunction decreased during the trial and were similar in the two arms.<sup>35,36</sup>

One of the major concerns about the expansion of circumcision services is the safety of the procedure. Common complications include bleeding, wound infection, and swelling. Adolescent or adult circumcision is a more complex procedure than when performed in infants, requiring suturing. In the three RCTs, complications were observed in 3–7% of HIV-negative men,<sup>13,37,38</sup> and in 6–8% of HIV positive men.<sup>13,38</sup> The majority of these were mild. In the Rakai trial safety increased with number of surgeries performed by the physician, where complications occurred in ~9% of procedures for the first 20 procedures declining to under 4% thereafter. Furthermore, physicians in the trials were provided with training, supervision, and adequate resources and this is likely to have contributed to the low complication rate in comparison to other settings.<sup>38</sup> There is scope for a higher risk of complications outside of trial settings. A systematic review of circumcision complications among men in Anglophone Africa showed that prevalence of complications varied widely (from 0% to 24%). Most of these were minor, but these risks are still a cause for concern.<sup>39</sup> Circumcision conducted by nonclinical providers can be associated with very high complications, as seen in a study among 562 adolescents from the Babukusu ethnic group in western Kenya, which found that 18% of men had a complication when the procedure was performed by a medical provider and when the procedure was performed traditionally the complication risk was 35%.<sup>40</sup> A sub-study in the same population directly observed 24 boys undergoing medical and traditional circumcision, respectively, and found that some boys experienced permanent adverse sequelae, including one very serious life-threatening case by a “medical” practitioner who was later found to have no documented medical qualifications. These results show that under nonsterile conditions, adolescent and adult circumcision can frequently be associated with severe complications.

National policies are needed to ensure the provision of adult male circumcision services which can be provided safely and efficiently, and WHO/UNAIDS have produced guidelines on provision of safe circumcision.<sup>41</sup> Neonatal or infant circumcision is a simpler and safer procedure than adult circumcision and therefore countries may choose to also expand services among younger boys as a longer-term HIV prevention strategy.

There are also concerns that risk compensation may occur following the expansion of circumcision services, where unsafe sexual practices among men increase, due to a belief they are protected from HIV infection. However, mathematical modeling suggests that considerable increases in risky behavior would be

required to override the protective effect of circumcision.<sup>42</sup> In the trials, there were few differences in reported sexual behavior by circumcision status<sup>13–15</sup> but these may not reflect patterns of behavior change during scale-up of circumcision for several reasons. Firstly, men enrolled on the trial were not aware that circumcision reduced the risk of HIV. Furthermore, the capacity to provide high quality behavioral counseling outside a trial setting will be challenging in already overstretched health services. Results from one study conducted outside a trial setting are promising: of 648 men from Western Kenya, those who elected to be circumcised reported similar risky sexual behavior following the procedure compared to men who remained uncircumcised.<sup>43</sup> However, this study was published prior to the results of the RCTs and further observational studies are needed in the current era to fully evaluate the potential issue of risk compensation. Further work to evaluate optimal counseling strategies in resource-poor settings is ongoing.

As a one-off procedure requiring no ongoing user-adherence, male circumcision is likely to be a cost-effective HIV prevention strategy.<sup>42,44</sup> For example, in the Gauteng Province, South Africa, where HIV prevalence is 25.6%, and the majority of men are currently uncircumcised, it is estimated to cost US\$181 per HIV infection averted, assuming all men were circumcised.<sup>44</sup> Ultimately this could save US\$2.4 million net over 20 years considering the costs averted through a decline in HIV incidence. In Rakai, Uganda, where HIV incidence is lower, authors estimated it would cost US\$2631 per HIV infection averted assuming 75% of males were circumcised.<sup>42</sup>

## Conclusions

Male circumcision is the only intervention to have proven efficacy against HIV infection in multiple RCTs. However, this protection is only partial (approximately 60%) and access to safe circumcision services accompanied by comprehensive behavioral counseling is needed. Further operational research is ongoing in southern and eastern Africa to identify the best method of integrating safe circumcision services into current health systems, as well as the development of relevant counseling materials.

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# 13

## Microbicides for Prevention of Sexually Transmitted Infections

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### Introduction

According to World Health Organization (WHO),<sup>1</sup> 480 million new cases of sexually transmitted infections occurred in the year 2005 around the world, in addition to HIV which was transmitted to about 2.7 million humans.<sup>2</sup> *Neisseria gonorrhoeae* accounted for around 87 million and Chlamydia for more than 101 million infections. Human papillomavirus (HPV) leading eventually to carcinoma of cervix is transmitted to 0.5 million women each year.<sup>3</sup> “Safe” sex is preached, counseling the use of condoms. These are however, not consistently used by men. The power dynamics of sexual relations and gender inequities prevent women from negotiating with their partners to use a condom. The female condom has yet to have acceptability of both the partners leave aside its cost and limited availability. In this scenario, Women’s Associations, particularly in USA, are urging the development of microbicides with the highest priority, and due to their demand and sustained campaign, NIH has provided generous grants to academia and industry to hasten the development of safe and effective microbicides. About 5 dozen candidate microbicides are in the pipeline. Though some are promising, none has completed all phases of clinical trials successfully against HIV to obtain final regulatory approvals for marketing to the public for protection against HIV and/or other STIs. However, few of these microbicides, passing through clinical safety trials, have the potential of protection against HIV, herpes simplex virus type-2 (HSV-2), gonorrhea, and *Chlamydia trachomatis* transmitted by sexual route. The most promising results are from Center for the AIDS program of research in South Africa (CAPRISA) 004 microbicide randomized trial, which showed effectiveness of topically applied Tenofovir Gel in prevention of HIV and HSV-2.<sup>4</sup> There were no serious adverse reactions. This has the potential to fill the gap in HIV prevention, especially for women who cannot negotiate other methods, such as condom use.

This chapter will summarize the information on the promising candidate microbicides and the rationale on which these are based.

### Definition

Microbicide literally means a product that kills microbes. When marketed for vaginal or rectal use, it should have the ability to kill a variety of pathogens that invade the vagina or rectum by sexual route. Microbicides are inserted by women and therefore only require passive acquiescence of men. Microbicides could be used alone, or in combination with a physical barrier such as condom, diaphragm, to provide increased protection or backup in case of barrier failure. Vaginal use products are usually in the form of creams/gels, pessaries, tablets, films, and sponges.

### Mode of Action of Different Microbicides

Microbicides exercise their action by a variety of ways:

1. by surfactant action dispersing on the membranes;
2. by creating and buffering the vaginal milieu to acidic pH nonconductive to survival and multiplication of pathogens;
3. by blocking the attachment and entry of a virus such as HIV into a host cell;
4. by preventing the integration of the virus;
5. by inactivation via a specific antibody;
6. by inhibiting replication of the virus/infecting microorganisms.

Some microbicides kill the invading microorganisms by yet to be elucidated mechanisms, others may act by multiple mechanisms.

### SURFACTANTS

A number of spermicides are available in the market enabling women to protect themselves against an unwanted pregnancy. A well-known product is Nonoxynol-9 (marketed as, “Today” by Johnson and Johnson). Nonoxynol-9 was also observed to exercise virucidal action on HIV. Hence, one of the first spermicides clinically tested for protection against HIV was a sponge based

N-9 formulation on which clinical trials were conducted. The trial gave the unexpected results of enhancing the transmission of HIV.<sup>5</sup> This was ascribed to inflammation and mucosal damage that N-9 caused to the vaginal epithelium.<sup>6</sup> Industry then tried to improve the characteristics of N-9 based vaginal use products. Excipients were included to cover the mucosal lining and confer bioadhesive properties. Also the release rate of N-9 was regulated to keep its concentration low in the vicinity of the vaginal epithelium. A gel containing N-9, made by a New York based company, with improved characteristics, which was considered safe IN phase-I clinical trials was taken up by UNAIDS initiative for multi centre phase III trials. The results of these trials were disappointing. The product failed to prevent the transmission of HIV by the sexual route.<sup>7</sup> Thus, N-9 based products, though numerous in the market, are unlikely to serve as safe microbicides against HIV.

### Protect Aid Sponge

Alexandre Psychoyos in Paris invented a sponge of polyurethane foam that was impregnated with a gel containing a combination of N-9, benzalkonium chloride (BZK) and sodium cholate, the bile salt.<sup>8</sup> Each surfactant was used at 25 mg/5 g of the gel. The N-9 content was thus 40 times lower than in “*Today*” sponge and BZK was 2.5 times less than in the pharmatex sponge. By decreasing the concentration of N-9 and BZK, it was hoped that the genital irritation effects of these 2 compounds will be substantially, if not completely removed. A third compound, of natural provenance, the bile salt sodium cholate was included so as not to diminish the spermicidal cum antibacterial action. The sponge conferred 100% protection against pregnancy in 20 young women over 1 year of use. Their sexual frequency was at an average 3 times a week. The gel used in the sponge was observed to have anti-HIV effect on the virus *in vitro*. No *in vivo* studies on prevention of HIV or other STIs have been reported.

### C31 G

It is an equimolar mixture of 2 synthetic amphoteric surface active compounds, which have broad-spectrum antimicrobial and spermicidal activity properties.<sup>9,10</sup> Its active agents are alkyl dimethyl glycine (coco betaine) and alkyl dimethyl amine oxide (cocoamine oxide), buffered with citric acid. The alkyl chain length of C12 to C16 resembles the fatty acids of coconut oil. Biosyn company has made a gel (SAVVY®) and a pessary containing C31 G, which are being projected as microbicides. The product acceptability of C31G, when tested for 1 week duration in women was found to be limited due to burning and heat sensation.<sup>11</sup> Trial conducted in 1562 women on SAVVY reported 3.6% higher reproductive adverse events as compared to placebo.<sup>12</sup> Another phase III double blind, randomized, placebo controlled trial in Nigeria has given disappointing results on SAVVY as it failed to reduce the incidence of HIV infection.<sup>13</sup>

### Sodium Lauryl Sulfate

It is another surfactant which was formulated as invisible condom by Universite Laval, Quebec, Canada. It can disrupt both enveloped as well as nonenveloped viruses.<sup>14</sup> It covers the vaginal wall as liquid at room temperature and then transforms into a gel at body temperature, thereby blocking transmission of HIV and other STIs.<sup>15</sup> It has been found safe in rabbit model and two phase-I clinical trials.<sup>16,17</sup> Results of phase II study in 200 cameroon women are pending.

### ACIDIC BUFFERS

The healthy vagina usually has a pH <4.5 due to the presence of lactobacilli in dominant numbers. This pH discourages the growth of many pathogens in the vaginal milieu. It may however, be pointed out that following intercourse, semen neutralizes the acidic milieu enabling the sperms to survive and reach the cervix. This window of neutral pH lasts usually for 2 hours before lactobacilli can make enough lactic acid to bring back the pH to 4. During this period, pathogens transmitted by the male partner can invade the target cells and get established. Keeping these dynamics in mind, a company in Baltimore, USA has patented a gel “BufferGel” made from a polymer, i.e., Carbopol 974P which buffers the pH to about 4. The composition of the gel is such that it can counteract the pH neutralizing effect of semen and thus maintain the pH in acidic range, which is noxious to both the sperms and many pathogens causing STIs. When tested in different animals for prevention of STIs and pregnancy, it showed 87% contraceptive efficacy in rabbits, and significant protection against vaginal and rectal transmission of HSV-2 and *Chlamydia trachomatis*. However, it did not protect against vaginal transmission of *Neisseria gonorrhoeae* in the mouse.<sup>18</sup> The use of BufferGel once or twice daily for 14 days caused no clinically significant change in number of probiotic lactobacilli resident in vagina.<sup>19</sup> This gel has gone through preclinical toxicology and also phase I clinical trials for safety and acceptability. BufferGel application twice daily for 14 days caused a decrease in the prevalence of BV from 30% at enrolment to 6% at 1 week and 7% at 2 weeks.<sup>20</sup> Daily application of BufferGel directly to the penis was found safe and well-tolerated by healthy low-risk and HIV-positive men.<sup>21</sup> Phase II/IIB multicenter trial was undertaken to determine the safety and effectiveness of BufferGel in preventing HIV transmission to women during sex. The results indicate that although the microbicide was safe, it did not have any protective effect against HIV or other STI pathogens.<sup>22</sup>

Another formulation under test, i.e., ACIDFORM which consists of gelling agents, buffer salts, humectants, preservatives, and water in a proprietary mixture. All ingredients are generally regarded as safe (GRAS) except for one, which is currently used in marketed vaginal formulations.<sup>23</sup> The gel caused no vaginal irritation or patient complaints when applied for 6 consecutive days.<sup>24</sup> Its antimicrobial efficacy against herpes and chlamydia

has been established in animal studies.<sup>25</sup> ACIDFORM when used with diaphragm daily for 14 days, appeared to be safe and acceptable in 69 low-risk abstinent women.<sup>26</sup> In a randomized, double-masked, single-center phase I study in circumcised and uncircumcised men to assess penile irritation, safety, and acceptability, use of ACIDFORM for 7 consecutive days gel compared with K-Y® Jelly, was found to be equally safe and well-tolerated by healthy low-risk men.<sup>27</sup> The effectiveness of ACIDFORM as compared with metronidazole gel was found to be significantly less in a double-blind clinical trial for the treatment of symptomatic bacterial vaginosis.<sup>28</sup>

In certain societies, naturally occurring acidic compounds such as lime juice have been used with limited benefit. Recent clinical trials evaluating lime juice have not found it free from toxicity.<sup>29</sup>

## VAGINAL MILIEU PROTECTORS

### Probiotics

Lactobacilli survive and colonise in various cavities and contribute as living sentinels to ward off infections. They secrete lactic acid which is responsible for keeping the pH of healthy vagina around 5. Acidic pH discourages the growth of several pathogens.<sup>30</sup> Several strains but not all, of lactobacilli also secrete around them H<sub>2</sub>O<sub>2</sub>, acting as local antiseptic.<sup>31</sup> Also secreted are peptides (bacteriocins) with antimicrobial properties. By virtue of their colonization, lactobacilli are believed to offer competitive exclusion for attachment of various pathogens.<sup>32</sup> It is obvious that lactobacilli act as local natural “microbicide” offering first line of defense against intruding pathogens. Lactobacillus colonization has been shown to correlate with decreased HIV proliferation.<sup>33,34</sup> Bioengineered lactobacilli (or “live microbicides”) are also being developed to express proteins that bind to HIV and block either viral–host cell fusion or viral entry into host cells. Three proteins expressed through this type of system are functional two-domain CD4,<sup>35</sup> a derivative of gp41,<sup>36</sup> and cyanovirin.<sup>37</sup> These live genetically engineered microbicides are all in preclinical development.

It follows that a good microbicide for vaginal use should be compatible with probiotic lactobacilli resident in the vagina. Not all microbicides developed or in process of developing have been tested for coexistence with lactobacilli.

The species of lactobacilli present in healthy human vagina have been identified in various countries. Vasquez et al.<sup>38</sup> reported the presence of *L. crispatus* in 47.8%, *L. gasseri* in 30.4%, and *L. jensenii* in 17.4% of 23 Swedish women examined. Vallor et al.<sup>39</sup> reported the predominant species as *L. jensenii* (41%) and *L. crispatus* (38%) in USA. Burton et al.<sup>40</sup> from Canada reported that out of 14 subjects harboring lactobacilli, *L. iners* was present in 8/14 (57.1%) and *L. crispatus* in 7/14 (50%) of women; these two species coexisted in 2 subjects. The above mentioned species of lactobacilli were relatively rare in their occurrence in India. The more frequent lactobacilli were *L. reuteri*, *L. fermentum*,

*L. salivarius*, and *L. plantarum* which together were present in 80% of Indian women.<sup>41</sup>

Though lactobacilli are predominant in healthy vagina, they are depleted/absent in women suffering from recurring episodes of bacterial vaginosis (BV) with vaginal pH  $\geq 5$ . In a study done in India, no cultivable lactobacilli could be isolated from 60% of the women. However, the remaining 40% harbored one or more strains of lactobacilli. This anomaly is explainable on the grounds that all strains of lactobacilli do not make high amounts of lactic acid. While both D and L-isomers of lactic acid are secreted by probiotic lactobacilli, it is primarily the D-lactic acid which contributes to low vaginal pH due to its inability to get further catabolized in human energy metabolic pathways.<sup>42</sup> It was found that the mean quantity of D-lactic acid produced by strains from vagina of women with BV is nearly half of the D-lactic acid secreted by the strains of the same species isolated from women with healthy vagina with vaginal pH  $\sim 4$ .<sup>43</sup> This property should be considered in selecting suitable probiotic strains of lactobacilli for replenishment of vaginal flora.

## INHIBITORS OF HIV ENTRY

### Polyanionic Compounds

#### PRO 2000

PRO 2000 (Indevus Pharmaceuticals, USA) is a synthetic, long-chain, naphthalene sulfonic acid polymer consisting of alternating 2-naphthalene sulfonic acid sodium salt and methylene units, a synthetic carbomer gelling agent, pH 4.5 buffer, and a combination of preservatives. These interfere with the virus adsorption process by disrupting the initial binding and membrane fusion steps of HIV-1 infection.<sup>44</sup> It binds to CD4 with nanomolar affinity and blocks binding of HIV gp120 to CD4. It inhibits infection by a wide range of HIV isolates in a variety of cell types. Phase I clinical trials in Europe,<sup>45</sup> the USA, and South Africa<sup>46</sup> showed that PRO 2000 was generally well-tolerated; however, at the highest concentrations tested (4%), it was associated with a slightly higher incidence of intermenstrual bleeding compared with placebo.<sup>47</sup> Clinical investigations are continuing with PRO 2000/5 alone (phase III) and a combination of PRO 2000/5 and BufferGel (phase II/IIB safety and efficacy study) for preventing vaginally acquired HIV infection.<sup>48</sup>

#### Cellulose Sulfate

Cellulose sulfate (Ushercell, Polydex Pharmaceuticals, Canada and Topical Prevention of Conception and Disease [TOPCAD], USA): Cellulose sulfate acts by binding with the V3 loop of the gp120 HIV-1 envelope, and it can inhibit both CXCR4 and CCR5-tropic virus for attachment.<sup>49</sup> It has contraceptive property<sup>50</sup> and in preclinical studies, it showed activity against HIV, HSV-1 and 2, HPV, *N. gonorrhoeae*, *Chlamydia trachomatis*, and *G. vaginalis* and no noxious activity



against lactobacilli.<sup>51–53</sup> Phase I safety studies on cellulose sulfate, which involved 518 women and 48 men, found the gel to be safe.<sup>54</sup> Two phase III efficacy trials of cellulose sulfate versus placebo were initiated in Africa and India, but both studies were halted in 2007 after interim analysis of one of the studies showed a higher HIV seroincidence than expected in the cellulose sulfate arm. Of 1425 women enrolled (717 in the cellulose sulfate arm and 708 in the placebo arm), there were 25 seroconversions in the cellulose sulfate arm compared with 16 seroconversions in the placebo arm.<sup>55</sup> The second phase III study was halted as a precaution because of safety concerns arising from the first trial.<sup>56</sup>

A number of other sulfated polymers have been tested. Sulfonated polystyrene, besides the expected antiviral invasion properties, agglutinates sperms and inhibits acrosin, blocking fertilization. Zanveld et al. have made formulations containing polysulfated styrene and cellulose for similar purposes.<sup>57</sup>

### Carraguard

Carraguard (Population Council, USA): David Philips at population Council Labs, New York was the first to point out that carragenins extracted from sea weed prevents the attachment of HIV from leukocytes to epithelial cells.<sup>58</sup> The extract is not only cheap but safe and is used in chewing gum with no observed toxicity. The test product named “Carraguard” is a gel formulation of a mixture of  $\lambda$  and  $\kappa$ -carrageenans derived from red seaweed.<sup>59</sup> It has gone through phase I and II extended safety trials where it was found to be safe and acceptable.<sup>60,61</sup> However, the phase III trial conducted to test the efficacy of Carraguard for prevention of HIV infection in women in South Africa did not show significant protection.<sup>62</sup>

### Cellulose Acetate Phthalate (CAP)

CAP blocks gp120 binding sites on HIV and also blocks CXCR4 and CCR5-tropic virus types in tissue explants and animal models.<sup>63,64</sup> It has shown *in vitro* activity against HIV-1, HSV-1, and HSV-2.<sup>65</sup> It is being developed as both a film and micronized gel. The micronized form has the advantage of providing acidic environment which causes disintegration and loss of infectivity of HIV-1.<sup>66</sup> Phase I trial of 13% gel was halted because of heavy vaginal discharge in all participants, attributed to the hyperosmolarity of glycerol based formulation.<sup>67</sup>

### Dendrimers

They are new anionic macromolecules containing a central core, interior branches and terminal surface groups adapted to specific targets; thereby binding to multiple locations on multiple cells. The first dendrimer tested clinically was SPL 7013 (Vivagel, Starpharma Holdings Ltd. Melbourne, Australia). It provided protection from simian/human immunodeficiency virus (SHIV) in macaque model and from HSV-2 in animal models.<sup>68,69</sup> It has

been well-tolerated in phase I safety trial in Australia on males<sup>70</sup> and another phase I trial in Kenya and USA is in progress.

### CCR5 Blockers

Another mechanism of preventing entry of HIV is by inhibiting CCR5; an important coreceptor for macrophage-tropic viral strains. One such inhibitor is PSC-RANTES, which exhibits *in vitro* antiviral activity against all strains of HIV and inhibits HIV-1 infection of Langerhans cells, crucial cells for HIV-1 transmission across the vaginal epithelium.<sup>71</sup> It protected macaques from SHIV SF 162 without any systemic toxicity/absorption.<sup>72</sup>

Another such antagonist is CMPD 167, a cyclopentane based compound formulated as 5 mmol vaginal gel. It provided protection from vaginal SHIV in eight of ten macaques.<sup>73</sup>

The drawback of using CCR5 blockers is their inability to block the entry of CXCR4-tropic virus. Though this pathway is less important in sexual transmission, prolonged use of CCR5 inhibitors may put pressure on HIV-1 to shift toward the use of non-CCR5 pathways/coreceptors to gain entry into host cells. An effective microbicide should block all modes of receptor mediated entry of HIV.

## ANTIMICROBIAL COMPOUNDS

### Magainins

These are a group of cationic peptides, 21 to 27 residues in length, isolated from the skin of African clawed frog (*Xenopus laevis*) and have antibacterial, antifungal, antiprotozoan, antiviral, and antispermatozoal action.<sup>74</sup> At low concentrations they inhibit the growth of numerous species of bacteria and fungi and induce osmotic lysis of protozoa. The peptides assume an amphibilic alpha helix structure in a hydrophobic environment and punch holes in the cell walls of infecting organisms.<sup>75</sup> Laboratory evaluation of magainin-A revealed that the peptide inhibits the growth of STIs but not HIV-1 and HIV-2.<sup>76</sup>

### Nisin

It is a cationic peptide of 34 amino acids and molecular mass of 3.5 kDa produced by the bacterium *Lactococcus lactis*. For the last 50 years, Nisin has been used as a food preservative throughout the world; hence, the WHO and the US Food and Drug Administration (FDA) have conferred GRAS (generally regarded as safe) status on the peptide.<sup>77</sup> Safety and contraceptive efficacy of Nisin was evaluated in rats, rabbits, and monkeys, and it was proposed that Nisin could serve as a safe vaginal contraceptive.<sup>78,79</sup> Repeated application of high dose of Nisin gel (15,150 microM/day for 14 days) on cervicovaginal epithelium of rabbits caused no abnormality in structural integrity of vaginal epithelium and no change was noticed in the cytokines from cervicovaginal lavage (CVL).<sup>80</sup>



## Novispirin G-10

A novel antimicrobial alpha-helical octadecapeptide structurally related to cathelicidins and other innate immunity peptides is reported to be useful to prevent chlamydial infection and/or rectify the abnormal vaginal flora associated with BV.<sup>81</sup>

## Defensins

These are peptides secreted by mammalian cells with unusually broad spectrum of action on gram-positive and gram-negative bacteria, many fungi, mycobacteria, spirochetes, and several enveloped viruses. They are amphipathic peptides with complex folding, rich in antiparallel beta-sheet and devoid of alpha-helical domains.<sup>82</sup>

## Docosanol

Also known as behenyl alcohol, docosanol is a 22 carbon saturated alcohol mainly used as an antiviral agent, specifically against HSV.<sup>83</sup> It inhibits viral replication by interfering with fusion or early intracellular events following viral entry into target cells.<sup>84</sup>

## Squalamine

It is an aminosterol isolated initially from the shark, but has since been chemically synthesized. It exhibits potent bactericidal activity against both gram-positive and gram-negative bacteria. It is fungicidal and also causes lysis of protozoa.<sup>85</sup>

## HUMANIZED MONOCLONAL ANTIBODIES

Antibodies of high affinity have exquisite capability of specifically recognizing a ligand or epitope present on microbes or sperms. In case antibodies are developed to critically important epitopes, they can inactivate and block the sperm function, and/or prevent infection by a given pathogen. Antibodies constitute a natural arm of the body's defence system. Hybridomas secreting monoclonal antibodies can easily be generated in mice. The mouse monoclonals are valuable reagents for diagnostics but cannot be used for therapeutic purposes due to sensitization of humans to mouse proteins. This barrier has been broken with the development of technologies enabling humanization of mouse monoclonals. A number of chimeric antibodies have received FDA authorization for therapy of chronic diseases and cancers. The high cost of humanized recombinant antibodies can be reduced substantially by their expression in plants.

Kevin Whaley at Johns Hopkins University has pioneered in assessing the utility of antibodies for use locally in vagina to control fertility and prevent transmission of pathogens. Data reported so far is of work done in experimental animals. They have also developed a controlled delivery system for long term release of antibodies for passive immunoprotection.<sup>86,87</sup> This is an

attractive approach as it simulates a physiological mechanism. It will however, be difficult to develop effective antibodies against the large number of microorganisms that invade the vagina.

## HIV REPLICATION INHIBITORS

Current microbicide research is focused on the identification and development of novel nondetergent spermicidal nucleoside and non-nucleoside inhibitors, aimed at preventing sexual transmission of HIV. A preclinical evaluation of TMC120 (4-[[4-[(2,4,6-trimethylphenyl)amino]pyrimidin-2-yl]amino]benzenecarbonitrile), a diarylpyrimidine, that was the first non nucleoside reverse transcriptase inhibitor (NNRTI), has shown it to have *in vivo* effectiveness as a topical microbicide in preventing HIV-I transmission in a humanized severe combined immunodeficient (hu-SCID) mouse model.<sup>88</sup> It is now being tested in several phase I and II trials. One formulation employs a slow release vaginal ring, which would allow for once a month, non-coitally dependent dosing.

## Tenofovir

Tenofovir disoproxil fumarate (TDF), a reverse transcriptase inhibitor, marketed by Gilead Sciences under the trade name Viread, was approved by the USFDA on October 26, 2001 for the treatment of HIV, and on August 11, 2008 for the treatment of chronic hepatitis B. A 2006 trial by the Family Health International, employed orally either tenofovir or placebo in 936 high-risk women in Cameroon, Ghana, and Nigeria. Overall, a total of eight HIV infections occurred in women in the study, including those randomized to receive Tenofovir or placebo. These infections were too few than initially estimated in the design of the study. Thus, data was insufficient to determine Tenofovir's effectiveness against HIV infection. Additional studies with more participants were required to determine efficacy.<sup>89</sup>

A topical gel form of Tenofovir (1%) was developed to prevent the sexual transmission of HIV. A phase IIb trial of 1% Tenofovir gel in South Africa sponsored by the Centre for the AIDS Programme of Research in South Africa (CAPRISA) on 980 women has been recently completed. HIV incidence in the Tenofovir gel arm was 5.6 per 100 women-years (person time of study observation) (38 out of 680.6 women-years) compared with 9.1 per 100 women-years (60 out of 660.7 women-years) in the placebo gel arm (incidence rate ratio = 0.61;  $p = 0.017$ ). In high adherers (gel adherence >80%), HIV incidence was 54% lower ( $p = 0.025$ ) in the Tenofovir gel arm. In intermediate adherers (gel adherence 50–80%) and low adherers (gel adherence <50%), the HIV incidence reduction was 38% and 28%, respectively. Tenofovir gel reduced HIV acquisition by an estimated 39% overall, and by 54% in women with high gel adherence. No increase in the overall adverse event rates was observed. There were no changes in viral load and no Tenofovir resistance in HIV seroconverters.<sup>90</sup>

Another efficacy trial is intended to compare oral pre-exposure prophylaxis with Tenofovir and a combination of Tenofovir plus emtricitabine, with topical use of Tenofovir gel.

## Serine Proteinases and Their Inhibitors

Inhibitors of serine proteinases are observed to inhibit replication of HIV without cytotoxicity.<sup>91</sup> The compound TLCK acts on both cell contained and cell-free virus. It also blocks fertilization presumably by inhibiting acrosin. Another synthetic inhibitor AGB (4-acetamido phenyl 4-guanidinobenzoate) has more potent contraceptive properties than the benchmark N-9 and has also a strong anti-HIV action.<sup>92</sup>

## COMBINATION MICROBICIDES BASED ON MULTIPLE MECHANISMS OF ACTION

### Polyherbal Microbicides

The ingredients employed are from plants which have been used for centuries by humans without any serious side effects. More than one active ingredient is employed in the formulation to act at different points, ideally aimed to prevent/cure a wide spectrum of RTIs and STIs.

#### Praneem Polyherbal Tablet (PPT)

It is a formulation composed of purified quality controlled extracts of Neem (*Azadirachta indica*) leaves, saponins from *Sapindus mukorossi*, quinine hydrochloride and *Mentha citrata* oil dispensed with excipients maintaining pH of the formulation at 4.<sup>93</sup> Leaves, bark, and kernel of Neem tree contain about 100 tri, tetra, and penta terpenoids, 25 of these are characterized chemically. They exercise a wide spectrum of action on fungi,<sup>94</sup> bacteria,<sup>95</sup> and viruses.<sup>96</sup> Neem extract stimulates immune responses particularly of Th1 type.<sup>96,97</sup> Saponins contribute to spermicidal and contraceptive property. Each component of the PPT has spermicidal properties, their combination is, however, synergistic and enhances the spermicidal activity by 8-folds.<sup>98</sup> Spermicidal action on human sperm is not only evident *in vitro* but also *in vivo*, as demonstrated by post coital tests.<sup>99</sup> In addition to killing of sperms, the migration of sperm to cervical mucous is inhibited by PPT to a better extent than by the N-9 containing pessary, "Today".<sup>100</sup>

PPT inhibits the growth of normal and penicillin resistant strains of *N. gonorrhoeae*. It also inhibits urinary tract *E. coli* (including multidrug-resistant [MDR] strains), *Candida tropicalis*, and *Candida krusei*.<sup>93</sup> PPT prevents the transmission by vaginal route of Herpes simplex virus type 2 and *Chlamydia trachomatis* in progestin sensitized mice as determined by researchers at Johns Hopkins University. Praneem was also found to exercise virucidal action against HIV-1 by the discoverer of the virus Nobel Laureate Françoise Barre Sinoussi and Annie David at the Institut Pasteur, Paris.<sup>93</sup> Phase I safety trials on PPT were conducted in 3 institutions in India. Seven consecutive days use caused

no damage to vaginal epithelium or had any effect on cervical cytology and metabolic and organ functions of recipients.<sup>101</sup> Extended Phase I/II safety study was carried out on PPT at the National AIDS Research Institute (NARI), Pune on a cohort of monogamous married women and professional sex workers. Fourteen consecutive day use of the tablet was well-tolerated, with no significant abnormality observed on colonoscopy.<sup>102</sup> The pre-coital acceptability of PPT by both partners was reported to be high.<sup>103</sup>

Praneem prevents the integration of HPV-16 in infected cervical cells. Twenty women molecularly diagnosed positive for HPV16 infection with or without low-grade squamous intraepithelial lesion (LSIL) were assigned to receive intravaginal, topical application of either Praneem tablet or placebo for 30 days excluding the days of menstrual period and were evaluated for persistence of HPV infection using HPV L1 consensus and HPV type 16-specific PCR. One course of Praneem resulted in elimination of HPV in 6 out of 10 (60%) cases. A repeat course in four patients with persisting HPV infection caused clearance of HPV in two additional cases resulting in an overall clearance in 80% as against a spontaneous clearance of 10% (1/10) seen in the placebo arm. The elimination of HPV DNA was found to be accompanied by marked improvement in cytological abnormalities of Praneem-treated patients.<sup>104</sup>

## BASANT

It is another polyherbal formulation developed by the workers at Talwar Research Foundation. It contains 95% pure diferuloyl methane (curcumin), purified extracts of Amla (*Emblica officinalis*), Neem leaf extracts, purified saponins from *Sapindus mukorossi*, purified Aloe vera powder and rose extract water. Curcumin has anti-inflammatory<sup>105</sup> and anticancerous properties.<sup>106</sup> It blocks the cancer pathway by downregulating the NF- $\kappa$ B activation<sup>107</sup> by suppression of I $\kappa$ Ba kinase and Akt activation.<sup>108</sup> These attributes are desirable in a microbicide to be applied in the vagina and cervix. Curcumin is safe and its intake at as high as 8 g every day for 3 months by humans causes no ill effects.<sup>109</sup> Curcumin also inhibits HIV-1 LTR directed gene expression and virus replication.<sup>110</sup> It inhibits HIV-1 and HIV-2 proteases<sup>111</sup> and also has inhibitory activity against HIV-integrase<sup>112</sup> thus preventing the viral DNA to become a part of the host cell. Barthelemy et al. showed that curcumin used at 10–100 nm concentration inhibited tat transactivation of HIV-1–LTR lacZ by 70–80% in HeLa cells.<sup>113</sup> Curcumin also inhibits UV-light induced HIV gene expression.<sup>114</sup> Curcumin selectively down regulates HPV 18 transcription as well as AP-1 pathway in HeLa cells. It also causes reversal of c-fos/fra-1 transcription to normal state in tumorigenic HeLa cells and can thus control transcription of pathogenic HPVs during keratinocyte differentiation and progression of cervical cancers.<sup>115</sup>

Antioxidant properties of amla are less due to ascorbic acid and more due to the polyphenols such as ellagic acid, gallic acid, and tannins.<sup>116</sup> El Mekawy et al. reported that the methanolic extract of the Amla fruit has an inhibitory effect on HIV-1 reverse transcriptase.<sup>117</sup>

Aloe vera has a soothing effect on mucosal linings and is reported to have wound-healing properties.<sup>118</sup> Fahim and Wang reported that 7.5% and 10% lyophilized Aloe was toxic to sperm tail causing immobilization of spermatozoa but produced no irritation or ulceration of rabbit vaginal epithelium.<sup>119</sup> It has a considerable inhibitory effect on HIV and HPV.<sup>120</sup>

Rose water extracted from rose petals has a pleasant fragrance and is used in perfumery preparations.

BASANT inhibits standard strains and clinical isolates of *N. gonorrhoeae* including those resistant to penicillin, tetracycline, ciprofloxacin, and nalidixic acid.<sup>120</sup> It also acts against *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida tropicalis* including strains resistant to fluconazole, Itraconazole and amphotericin B. It prevents entry of HIV-1 in P4-CCR5 cells and inhibits the replication of NL4.3 HIV in CEM-GFP and P4 cells, EC<sub>50</sub> = 1:20,000 dilution.<sup>120</sup> It also inhibits transduction of HPV 16 in Hela cells.<sup>120</sup> BASANT inhibits *Chlamydia trachomatis* both pre and post infection.<sup>121</sup>

BASANT was found nontoxic to human vaginal tissue and did not induce inflammatory cytokines. It effectively inhibited the entry and replication of both T-tropic and macrophage-tropic HIV-1.<sup>122</sup>

BASANT is currently in phase II clinical trial at Chitranjan National Cancer Centre, Kolkata in women with cervical dysplasia molecularly positive for HPV 16/18 with the idea of determining whether 30 applications of BASANT can eliminate HPV and regress early cancerous changes.

Another Phase IIb trial is in progress at the All India Institute of Medical Sciences and Sir Gangaram Hospital New Delhi in women with recurring episodes of Vaginitis/vaginitis, with vaginal pH >5. The prevailing infection is treated with BASANT followed by administration of probiotics. A combination of BASANT with three strains of Lactobacilli (*Lactobacillus fermentum* TRF#36, *Lactobacillus gasseri* TRF#8, and *L. salivarius* TRF#30) was found to be highly beneficial in these women. Seven to 14 days intake of BASANT plus probiotics intravaginally cured the prevalent infections and prevented their recurrence. It also restored the pH of vagina to normal acidic range. The cited strains of probiotics were selected on the merit of their high capacity for production of D-Lactic acid, their colonization potential in the vagina, their ability to secrete hydrogen peroxide around them, and their possession of Arginine deaminase preventing the production of foul odor. All strains were initially isolated from eco healthy vagina.

Microbicides discussed above have largely been tested in women for their ability to prevent transmission by heterosexual vaginal route. Intercourse by rectal route is more vulnerable. The rectal mucosa consists of one layer of columnar epithelium, and the subepithelial lamina propria contains many cell types to which HIV binds. Rectal lymphoid follicles contain M cells, which bind and present HIV-1 to underlying lymphoid tissue.<sup>123</sup>

Circumcision lowers significantly (50–76%) the transmission of HIV from infected women to their male partners, as observed in more than one trial in Africa.<sup>124–126</sup> This is understandable on the grounds that foreskin of the penis harbors macrophages expressing CD4 receptors and dendritic cells carrying intercellular adhesion DC-SIGN molecules.<sup>127</sup>

## Conclusion

Many of the formulations were primarily tested for preventing HIV transmission. Four microbicides namely, COL-1492, Carraguard, cellulose sulfate, SAVVY which did reach the phase III stage were not able to provide any significant protection against HIV. Some, contrary to expectations, even enhanced HIV transmission owing to the damage that they caused to the mucosal lining and vaginal epithelium. At present, ongoing phase III/IIB trials against HIV are on (i) Pro 2000/5, (ii) Pro 2000/5 in combination with BufferGel, (iii) Tenofovir gel (1%), and (iv) Tenofovir in combination with emtricitabine. The emerging trend is to use combinations rather than single active compounds. Intervention at more than one point is likely to result in better efficacy. Furthermore safety tested on a limited number of subjects as per standard format of phase II may not be sufficient to guarantee the safety on a larger number of subjects or with use of the product for a longer period. Better clinical trials protocols are being drawn in light of the past experience.

HIV is in fact not the only infection transmitted sexually. Infections due to *N. gonorrhoea*, Chlamydia, HSV, and HPV are transmitted in much larger numbers. It is in this context that efforts are also being directed to develop microbicides preventing reproductive tract infections and other STIs. This chapter summarizes the variety of compounds and formulations being developed. Those currently under clinical trials, after thorough preclinical studies are described in Table 13.1.

Attention has been drawn to the innate defense accorded by resident probiotic lactobacilli in vagina. A conjoint use of microbicide and probiotics is recommended for reproductive health and prevention of STIs.



**Table 13.1:** Microbicides of Interest Currently Under Clinical Trials

Active principle (Name)	Developed by	Mode of action	Status
Sodium lauryl sulfate (invisible condom)	Universite Laval, Canada	Surfactant, spermicidal, nonspecific disruption of enveloped and non-enveloped viruses	Phase II/III efficacy trials for protection against HIV
ACIDFORM (Amphora)	Instead Inc, USA	Spermicidal, acidifying agent	Phase III trials in progress with diaphragm for prevention of <i>N. gonorrhoeae</i> and <i>C. trachomatis</i>
Carbopol 974P (BufferGel)	ReProtect, USA	Spermicidal, acidifying agent	Phase II/IIb trials against HIV in progress
Naphthalene sulfonate (PRO 2000)	Indevus Pharmaceuticals, USA	Anionic polymer Negative charge interferes with attachment of HIV to CD4+ cells	Phase III for prevention of HIV in women
(PRO 2000/5 + BufferGel)	Indevus Pharmaceuticals + ReProtect, USA	Polyanionic + acidic buffer	Phase IIB safety and efficacy trials against HIV in progress
Dendrimers: SPL 7013 (Vivagel)	Starpharma, Melbourne	Entry inhibitor, protects against SHIV and HSV-2 in monkeys	Found safe in phase I studies in Australia; phase I in USA and Kenya planned
Tenofovir (Viread)		Nucleotide analogue; Reverse transcriptase HIV replication inhibitor	Two Phase IIB trials in progress: (i) 1% Tenofovir gel; (ii) oral Tenofovir + Emtricitabine vs. 1% Tenofovir gel
Diarylpyrimidine (TMC 120)		Non-nucleoside analogue; Reverse transcriptase inhibitor	Phase I/II trials in progress
Thiocarboxanilide (UC 781)		Non-nucleoside analogue; Reverse transcriptase inhibitor	Phase I trial in progress
Praneem Polyherbal tablet (PPT)	Talwar Research Foundation, Panacea Biotec	Multiple mechanisms; Prevents HIV replication and HPV integration	Phase II study for elimination of HPV-16/18
BASANT	Talwar Research Foundation	Multiple mechanisms; prevents entry, replication, and integration of T-tropic and M-tropic HIV; inhibits entry of HPV	Phase IIB trials for elimination of HPV-16/18
BASANT + Probiotics	Talwar Research Foundation	Wide-spectrum antimicrobial action of BASANT + restoration of healthy microflora and defense by lactobacilli by virtue of production of H <sub>2</sub> O <sub>2</sub> , lactic acid, and bacteriocines	Phase II/III trials indicate cure of vaginosis/vaginitis & restoration of vaginal pH to acidic range

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# Information and Communication Technologies to Support HIV and STI Care in Developing Countries

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# 14

## Introduction

The Internet, personal digital assistants (PDAs), cell phones, and other innovative technologies are part of a growing arsenal in the global effort to prevent and control HIV and other sexually transmitted infections (STIs). Appropriately utilized technologies may improve HIV/STI screening, prevention, surveillance, and care for patients and populations. In this chapter, we review the published literature regarding the use of information and communication technologies (ICT) to support HIV and STI with a particular focus in developing countries.

We will start by describing the two applications that we consider have the most potential to support HIV and STI care in developing countries: mobile devices and the Internet. Then we will describe some notable examples of information systems used for clinical care in developing countries. Finally, we will present how ICT are supporting education and professional development for healthcare workers treating HIV/STIs in developing countries.

## Mobile Health to Support HIV and STI Prevention and Care

Mobile health (medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, PDAs, and other wireless devices) has tremendous potential to support HIV and STI care and is currently demonstrating its impact. In particular, the use of short text messaging (SMS) provides many options for public health interventions.<sup>1</sup> For example, text messaging can be used for:

- Sending information to patients
- Gathering information from health personnel and patients
- Getting answers to questions
- Connecting people to people
- Performing transactions

### SENDING INFORMATION TO PATIENTS

This is the simplest way to use SMS.<sup>2</sup> Patients could receive messages from an institution such as a healthcare organization,

clinic, hospital, university, etc. Patients do not need to respond necessarily to the messages. They can just read the text they receive. Three specific applications are described below:

### Educating Patients

Cell phone text messaging can be used for educating patients about sexual health. For example, the San Francisco Department of Public Health currently uses SMS to promote sexual health by sending messages about HIV and STI to adolescents.<sup>3</sup> Mobile devices displaying soap opera videos, could be used also to reduce young urban women's HIV sex risk.<sup>4</sup>

### Notifying Patients

In this case, an institution sends messages whenever is needed, not on schedule. These messages may contain urgent information, such as a critical laboratory result. However, the notifications do not need to be urgent. For example, cell phones can be used for partner notification. In Australia, a website allows patients diagnosed with an STI to send an SMS or e-mail to partners who may have been exposed.<sup>5</sup> Regarding provision of test results, SMS sent to patients with *Chlamydia trachomatis* infection in a health clinic resulted in a decreased time to treatment of the infection.<sup>6</sup>

### Reminding Patients

Mobile phones can be used to send reminders. In this case, the person receives a text message on his/her mobile phone without any need to reply. The reminder could be about remembering to take antiretroviral therapy (ART) each morning (with the aim of increasing antiretroviral adherence). For example, Puccio and colleagues developed a program that used cell phone reminders to improve adherence in HIV-infected adolescents and young adults who were either going to begin an ART regimen for the first time or begin a new ART regimen.<sup>7</sup> In a systematic review conducted by Wise and Operario, four out of eight studies showed that patient adherence to ART was significantly improved with the use of electronic reminders as a stand-alone adherence strategy, but data on



the improvement of virological or immunological outcomes were not clear. At the moment, there is not enough evidence to demonstrate the effectiveness of medication reminders in HIV positive patients.<sup>8</sup>

In a simulation model of effective medication adherence improvement strategies, electronic reminders were found to be the least expensive of all adherence strategies, with an approximate monthly expense of \$50.<sup>9</sup> Therefore, more research is needed in order to establish a conclusive statement on the effectiveness of electronic reminders. In the meantime, more promising research is coming from developing countries. For example, in Peru, the Cell-Pos computer-based system uses cell phones and the Internet to enhance adherence to antiretroviral treatment (via SMS reminders) and to support HIV transmission risk-reduction among adults living with HIV/AIDS.<sup>10</sup>

Preliminary research by Curioso from the Cell-Pos project demonstrated that participants were receptive to the idea of receiving reminders via SMS, but specified certain characteristics they wanted the messages to have (such as being simple and concise). It was also important that the messages maintained confidentiality and privacy by using coded words or phrases (e.g., “Remember, it’s time for your life”) instead of “sensitive” words (e.g., HIV or antiretroviral). Patients wanted healthcare SMS that appropriately notified them, delivered a carefully crafted message, and appropriately ensure privacy, security, and confidentiality.<sup>11</sup> Cell phones are being used by the Cell Life project to support patient treatment adherence in South Africa.<sup>12</sup> Similarly, a cell phone system is being used in Rwanda to connect a large percentage of HIV clinics, improving reports of antiretroviral drugs stocks.<sup>13</sup>

Cell phones have also been used to reduce nonattendance to health clinics (through appointment reminders). Dyer and colleagues (2003) found that missed appointments decreased by 8% when SMS reminders were implemented in a London sexual health clinic.<sup>14</sup> A study conducted in Australia with outpatient clinics found that patients reminded of their appointment by SMS were significantly less likely to miss an appointment than a control group.<sup>15</sup> In a study conducted at John Hunter Clinic for Sexual Health in London, Price et al. showed that the use of text appointment reminders to increase utilization of clinic resources was efficient, cost-effective, and acceptable to patients.<sup>16</sup>

Future research on electronic reminders may include the development of software packages designed to support, educate, and remind patients about their treatment regimens. New advances in technological development could transform text reminders into multimedia messages that include realistic images of the medication to be taken (or other preferred images), support messages, and interactive elements.<sup>8</sup>

## GATHERING INFORMATION FROM HEALTH PERSONNEL AND PATIENTS

### Collecting Data from Health Personnel and Patients

This feature could be implemented through interactive voice response (IVR), data entry using key pads, or via SMS. An example

of data collection using ICT is Cell-PREVEN, a pilot project within a large randomized trial of 20 cities called PREVEN, which sought to lower STD rates in Peru.<sup>17</sup> Cell phones were exclusively used to report adverse events to metronidazole treatment among sexual workers. Health workers reported in real time to the system via IVR. If an adverse event was reported, the central system sent e-mail and SMS alerts to the researchers. Donald et al. from the Cell Life project found that cell phones made the recording of data very efficient, saving time, reducing the risk of losing patient notes and reducing potential breaks in confidentiality.<sup>18</sup>

Other mobile devices such as PDAs are frequently used for data collection. For example, Colecta Palm was a pilot project that involved the use of PDAs to enhance adherence to antiretroviral treatment and to support safer sex and HIV transmission risk reduction for people living with HIV/AIDS.<sup>19</sup> The pilot showed that PDAs could be a culturally appropriate way to approach and support people living with HIV and AIDS (PLWHA) in Lima.<sup>19</sup> In addition, low-cost PDAs have been used to collect sensitive sexual behavior data in Peru from young men and women, within the PREVEN study mentioned above, with very high acceptability.<sup>20</sup>

Additional promising open-source platforms could be used to develop data collection tools for mobile devices.<sup>1</sup>

## Journaling by Individuals

People can send SMS to keep a personal journal related to their health behavior. For example, a person can keep track of his/her diet by texting the number of calories consumed or the steps walked each day if the person is monitoring his/her exercise patterns. Diary entries, or active requests, via SMS have worked well in motivated and self-efficacious patients because mobile phones are a part of people’s everyday lives.<sup>21</sup> A mobile phone-based service would allow a health provider instantly to view which clients are creating daily entries.<sup>22</sup> This would act as a screening device, by revealing which patients are motivated and allowing for more time and effort to be spent on the less motivated patients.<sup>22</sup> One of the disadvantages of this feature is that it is mainly designed for individual use, not for large-scale data analysis by health organizations.<sup>2</sup>

## GETTING ANSWERS TO QUESTIONS

### Getting Answers from a Database

People can ask questions related to health using texting. When they get a response, they receive an answer from a database. One of the advantages of this feature is convenience. Sometimes the phrasing of the messages needs to be changed so that users are more likely to continue using the system. Services need to be in touch with the community they serve in order to create services that are spread via social networks and recommendations from friends. SexInfoSE, based in San Francisco, uses social marketing to advertise an SMS-based risk assessment for STI. For example, if your condom broke and you don’t know what to do, you can

text “sexinfo 1” to 61827 in San Francisco, then the service SexInfoSF.org<sup>23</sup> gives you the following information: “U may b at risk 4 STDs + pregnancy S.E.Clinic, Keith at Armstrong St, 415-671-7000 M-F9-5, W8-12, City Clinic 356 7<sup>th</sup> St 415-487-5500 MWF 8-4 TuTh -4.”<sup>23</sup>

Another advantage is privacy (or perception of privacy), because the person can request the information without being noticed. One of the main disadvantages is the 160-character limitation of SMS. This issue could be frustrating because people may not receive enough information or even the correct information. Another potential limitation is that the patient might need to know in advance the phrasing of the question they hope to receive an answer to (or be able to select it from a list of options).

### Getting Answers from a Real Person

People can send a sexual health question using SMS and receive an answer back from a real person (e.g., a doctor or a nurse), not a computer.<sup>2</sup> In this case, a doctor or a nurse may give more appropriate answers than a computer. One of the advantages is that organizations such as hospitals or clinics can set up specific days for this kind of services. One of the considerations is to adequately train health personnel on how to use SMS. Health personnel might even use regular computers connected to the Internet to send and receive the incoming questions. As one of the counselors in the Cell-Life project mentioned<sup>18</sup>: “The cell phones have made a big difference, as it’s easy to reach a client and they can phone me anytime if they have problems.” One of the main disadvantages is the cost involved in the operation of the system by health personnel. In addition, privacy and confidentiality issues need to be carefully addressed.

### CONNECTING PEOPLE TO PEOPLE

Social networks are very popular nowadays. For an effective provision of care for chronic conditions, including HIV, it is necessary to engage the patient and the community which supports him or her.<sup>24</sup> Two specific uses follow below.

#### Connecting Individuals

Physicians and patients can interact via texting. In fact, text messaging is an easy and, many times, a convenient way of allowing patients to keep in touch. Doctors can improve communication with patients using SMS.<sup>25</sup> For example, patients could report adverse events to their doctors using text messages. In addition, peer educators can stay connected with HIV patients and friends can support friends.

#### Connecting Groups

Text messaging supports one-to-one conversations as well as many-to-many discussion.<sup>2</sup> One of the best examples is Twitter, which was launched in 2007. Group support has long been an important strategy in changing health behavior, and now

increasingly SMS facilitates group interactions.<sup>2</sup> In fact, support groups, discussion threads, and collective action are now all possible using regular phones and text messaging.<sup>2</sup> This feature needs to be further explored in future studies.

Project Zumbido in Mexico aims to record the usage patterns and evaluate whether a system using mobile phones with unlimited text messaging helps to increase the level of social support experienced by HIV positive patients of an antiretroviral clinic.<sup>26</sup>

### PERFORMING TRANSACTIONS

#### Getting Things Done

This is an emerging use of texting. In this case, people can set up clinic appointments, register for peer activities at the clinic, or at the gym, etc.<sup>2</sup>

Three key issues related to the use of cell phones for healthcare are health data privacy, security, and confidentiality. Indeed, these issues are applicable to every stage of the use of cell phones for healthcare, including capturing personal health-related data from a cell phone, uploading it to a server, transmitting it to a web-based or other form of electronic personal record or medical record, using the data for interpretation and professional judgments in the care of that individual, and responding back to the person via, for example, an SMS message. Another concern is that while a cell phone might be used predominately by a specific person, it may occasionally be shared or left unlocked in a purse, on the table at home, or on the desk at work.<sup>27</sup>

### Role of the Internet to Support HIV and STI Prevention and Care

The Internet constitutes a potential source of information in healthcare (more than 43% of Internet users have used the Internet to seek health information). Patients can search for information about their diagnosis, seek out healthcare providers, and explore treatment options.<sup>28</sup> However, the Internet can also be used to solicit sexual partners.<sup>29</sup> Men who have sex with men (MSM) is a population that more actively seeks online sexual partners, at a rate approximately 7 times more frequently than non-MSM.<sup>30</sup> Seeking sexual intercourse on the Internet is a risk factor for HIV and STI transmission.<sup>31–33</sup> Individuals who seek sex partners through the Internet may report a higher level of sexual risk behaviors such as higher number of partners, more anal sex, and more sexual exposure to partners known to be HIV positive compared to those who do not use the Internet to find sex partners.<sup>31</sup>

Studies of patients of STI clinics also found that among this core group, the Internet is a common venue for meeting and having sex with partners. In San Francisco, MSM with early syphilis infections reported the Internet as the most common place to meet sex partners, followed by bars, bath-houses, and sex clubs.<sup>34</sup> Having sexual intercourse with partners met online has also been directly linked to syphilis epidemics and HIV transmission;

in 2000 Klausner et al. reported a syphilis outbreak among gay men linked to an online chat room in San Francisco<sup>35</sup> and in 2003 Tashima et al. reported two cases of acute HIV infection acquired through meeting persons over the Internet.<sup>36</sup>

### INTERNET AS A MEDIUM TO DELIVER PREVENTIVE INTERVENTIONS FOR HIV/STI

Internet interventions have proven to be an efficacious method of delivering health-related information to a large number of people who report high-risk sexual behaviors and who would not otherwise seek care or be targeted for health related interventions.<sup>30</sup> Several approaches, including the creation of educational sites, appealing banner advertisements tailored to the participants, online partner notification, online counseling sessions, and online STI testing, have met with a certain amount of success.<sup>37,38</sup> However, effective strategies to retain participants enrolled on the Internet need to be studied, especially in longer follow-up studies. In 2004 Bull et al. lost 85% of participants to follow-up in a 3-month online longitudinal study<sup>39</sup> and in 2006 Bowen et al. lost 21% of participants in a 1-week online randomized controlled trial (RCT).<sup>40</sup>

Compared to noncomputerized methods of data collection, Internet-based surveys have the advantages of automated randomization of persons and questions, automated branching, calculation of complex algorithms, consistency checks, automated data collection, and easy inclusion of graphics, video, audio, and animation.<sup>41</sup> Additionally, it is easier to identify patterns predictive of nonintentional and inconsistent responding, logical impossibilities, and inconsistencies that may increase the internal validity of the studies. The Internet provides participants with the ability to access the survey at any time, which may increase the participation of people who do not respond through traditional approaches.<sup>41</sup> Furthermore, given that most Internet approaches ensure the anonymity of the participants, responses are less likely to be distorted in the direction of social desirability, which may improve the sensitivity of studies of HIV-risk related behaviors.<sup>41</sup> Regarding data quality, Internet data collection yields very few missing data points and avoids data transcription errors because the information collected can be exported directly to a statistical software program.<sup>41,42</sup>

### Online Videos, Instant Messaging, and E-mail Reminders

Video-based offline and online interventions have been proven effective in decreasing risk behaviors for HIV and in reducing STI acquisition.<sup>43,44</sup> An RCT among patients attending public STI clinics in the US found that participants assigned to a theory-based 23-minute video had significantly fewer STIs compared with a standard waiting room environment.<sup>43</sup> Another intervention conducted on the Internet found that MSM exposed to an online 9-minute video drama were 3 times more likely to disclose their HIV status to their sexual partners than MSM not

exposed to the intervention.<sup>44</sup> Video interventions are effective for several reasons: (i) they combine auditory-verbal and visual presentations and thus are more engaging to the participants; (ii) they can easily integrate behavioral theories and can display characters to whom participants can relate; (iii) most computers have the necessary software to display them; and (iv) once programmed, they require only minimal staff time.<sup>43,45</sup>

Another tool that is used for health interventions is human instant messaging in chat rooms. This tool has been used for several purposes: to recruit hidden MSM populations (e.g., Hispanic MSM in the US), to perform online interviewing and to provide HIV counseling sessions to high-risk populations.<sup>46,47</sup> Interestingly, over the last several years robots that perform automated online conversations have been developed. In 2008, Stieger et al. created a dynamic Internet-based automatic interviewing program via the instant messaging service. This program can perform multiple interviews simultaneously and the interviews can be branched, which means that each question depends on the answer given to the previous one.<sup>48</sup> An online address book offers the possibility of validating demographic data in order to evaluate data quality.<sup>48</sup> Also, Microsoft, in collaboration with the Ministry of Health in Spain, developed a robot called Robin; this robot is able to answer questions from adolescents about sexual and reproductive health 24 hours a day, 7 days a week and can be added as a contact in Windows Live Messenger.<sup>49</sup>

Other tools that have been used for HIV prevention are e-mail and cell phone text messaging. E-mail has been used for recruitment, retention, and partner notification. Bull and colleagues used e-mails for recruitment and retention in an Internet-based intervention oriented to increase condom use and HIV testing among MSM.<sup>39</sup> Wang and colleagues recruited MSM through e-mails in order to compare their profile with MSM contacted through chat rooms.<sup>50</sup> Regarding partner notification, participants of an Internet chat room were notified via e-mail messages about a syphilis cluster and were encouraged to seek medical evaluation.<sup>35</sup> The InSPOT website allows newly diagnosed patients with an STI/HIV infection to inform anonymously or confidentially their partners through an electronic postcard that they might have been exposed to an STI or HIV.<sup>51</sup>

### STUDIES FROM DEVELOPING COUNTRIES

In Latin America, Internet access is growing fast along with the use of the Internet as a tool to provide HIV preventive educational material.<sup>52</sup> The use growth from 2000–2009 in Central America, South America, and the Caribbean was 913%, 838%, and 1,534%, respectively.<sup>53</sup> Some examples of the use of the Internet for prevention are the creation of online educational sites oriented toward improving the knowledge of local healthcare providers about the HIV epidemic in Brazil, Russia, and Vietnam<sup>54–56</sup>; websites oriented toward educating the youth about the risk factors for HIV acquisition and the different modes of protection in Mexico, the Philippines, Nigeria, and South Africa<sup>57–61</sup>; online counseling sessions about sexual and reproductive health topics



in the Philippines and the use of subsidized computer access at commercial cybercafés as a mechanism to attract the young population in South Africa.<sup>60,61</sup> The Internet has also been used to provide young gay men with messages about HIV prevention and a better knowledge about their rights in Guatemala<sup>62</sup> and to build networks of MSM in areas with high discrimination against homosexuality such as the Caribbean.<sup>63</sup> In Brazil a website was developed to inform health and security staff of the penitentiary system about prevention and assistance programs related to HIV/AIDS,<sup>64</sup> and in China an online survey was used to assess knowledge and sexual risk behaviors for HIV/STI among MSM recruited from gay venues.<sup>65</sup>

Internet cafes or “cabinas publicas” may be an effective means for delivering low-cost prevention messages to a great number of people, especially those who are not being reached using more traditional methods.<sup>66</sup> Two interesting studies conducted in Peru have used the Internet for delivering HIV prevention interventions. In the first study, Internet showed to be an effective tool to reach an important group of high-risk MSM who are not being reached by traditional interventions and have not been tested for HIV. The study also showed that free HIV testing can be effectively utilized as an incentive for participation.<sup>67,68</sup>

The second study is a web-based RCT to assess the effect of a 5 minute health promotion video compared to a text-only intervention in increasing rates of HIV testing among MSM. The videos were customized for two audiences based on self-identification: either gay or non-gay men. The mean time of follow-up was 125.5 days (range 42–209 days). The conclusion of this study was that the health promotion video oriented to non-gay-identified MSM was effective in increasing HIV testing in this population, although the percentage of clinic attendance was only 11%. No effect was seen in the video oriented toward gay-identified MSM.<sup>69</sup>

## Information Systems for Public Health and Clinical Care in Developing Countries

Research projects are ongoing in several developing countries to build an infrastructure for national health information systems.<sup>70</sup> The experience working with electronic health records is limited in these countries because of structural deficiencies as well as considerable deficits in social policies, particularly those related to public healthcare.<sup>71</sup> A recent review reports that some researchers assume data collected in developing countries are incomplete, inaccurate, unreliable and not timely due to lack of personnel training, lack of quality control, and hardware and software compatibility.<sup>72</sup> Therefore, it is an increasing necessity to strengthen the health management information system in developing countries.

Several papers have described the experience of working with electronic health records. Some of them focused particularly on the implementation methodology, potentialities, description, and essential requirements,<sup>73,74</sup> reporting declines in registration errors, identification of absentees, and detection of risk factors

and complications. Other papers have reported the process and programmatic action of evaluation and management systems,<sup>75–77</sup> including extraction of selected information, identification of risk factors, and compliance monitoring. Finally, other reports have dealt with clinical decision-making support systems, particularly in chronic diseases.<sup>78,79</sup>

In the context of HIV/AIDS, the necessity of monitoring patient status and assessing treatment effectiveness requires methods to make information readily available and to facilitate adherence to guidelines.<sup>78</sup> In this part of the chapter, we review some experiences of using information systems for HIV/STI diagnosis, clinical management and provider training in resource-constrained settings.

## ELECTRONIC HEALTH RECORDS

Electronic health records have evolved rapidly, particularly in chronic disease management, due to the necessity of strategies to follow-up patients without generating excessive paperwork. These records can provide data for continuous quality improvement not only at the individual patient level, but also at the health system level.

In Peru, the Almenara Hospital, part of the Health Social Security System, has had a computerized registry for all inpatient and outpatient visits of HIV-infected individuals since mid-1990s. Through this system, basic data are collected such as demographic information, date of clinic visit, date of hospital admission, as well as diagnosis and treatment.<sup>80</sup>

In Zambia, Stringer et al. developed an electronic patient tracking system. The system tracks program performance indicators, tabulates pharmacy dispensation data, and generates lists of late patients needing follow-up. Late patients are sorted by their last CD4 cell count, so that priority can be given to tracking those who are most ill.<sup>81</sup>

The Academic Model for Prevention and Treatment of HIV/AIDS (AMPATH) is sub-Saharan Africa's first electronic health record system for the comprehensive management of HIV-infected patients.<sup>82</sup> It was the first system to offer comprehensive ambulatory HIV care in Kenya, and the health record system is currently in use in several countries in eastern Africa.<sup>83</sup>

Advances in electronic medical records have permitted using computerized clinical reminders to improve adherence to established clinical guidelines and alert health providers when an action is recommended.<sup>84</sup> In HIV care, these types of reminders were associated with opportune initiation of clinical practices.<sup>85</sup>

Lober et al. have developed and implemented an EMR that supports both individual and population healthcare of HIV-infected patients in Haiti since 2005. The system is now implemented in about 40 sites nationwide providing ART, and includes records for about 18,600 patients.<sup>86</sup>

Fraser et al. have described an electronic medical record system (HIV-EMR) to support HIV and tuberculosis treatment in remote areas of Haiti.<sup>87</sup> This system permits medical doctors to order drugs and laboratory tests and provides alerts according



to clinical status and test results. In rural Rwanda, Partners in Health has implemented the HIV-ERM system based on the OpenMRS architecture (HIV-EMR 2.0).<sup>88,89</sup>

In Malawi, the Baobab Health Partnership has developed an information system that has been used to issue nationally unique IDs to more than half a million patients across 3 urban sites. The system uses an innovative touch screen interface and also supports both voluntary counseling and testing and ARV treatment.<sup>90</sup>

Recently, Nucita et al. reported an electronic medical record system developed by the DREAM Project in sub-Saharan African countries. Today the DREAM software hosts data from more 73,000 patients and it is used in 10 countries in sub-Saharan Africa by thousands of professionals and is now in its fourth version.<sup>91</sup>

In the Peruvian PREVEN study, a web-based electronic report system for STI allows interviewers to enter their data directly and check past laboratory test results and medication prescriptions in real time.<sup>92</sup> NETLab is a web-based lab result registration system that allows patients and healthcare providers to access lab results, and affords decision and policy makers and lab managers' mechanisms to assess the speed and accuracy of lab results. NETLab was fully implemented in 2007 and national data are available in the database. The laboratory information system allowed connectivity of the 24 regional laboratories in the country and secure, password-protected access to results for all health professionals and many patients (especially HIV patients). In 2007, 112,086 laboratory tests had been registered and there are 950 people living with HIV and 1,269 health workers actively using the system.<sup>93,94</sup>

Health information technologies can help HIV-infected patients to manage their therapy regimens by themselves. Previous reports have demonstrated that web-based support sites can be useful for people living with HIV/AIDS by creating virtual support or affinity groups. Examples include VIHrtual Hospital, a telemedicine web system for improving integral care at home for chronic HIV patients via Internet<sup>95</sup>; CREAIDS (Center of Reference for AIDS), designed to improve adherence to ART<sup>96</sup>; and CARE+, created to support adherence to medication and HIV transmission risk reduction.<sup>97</sup>

## TELEHEALTH AND TELEMEDICINE

The terms telehealth and telemedicine have been used interchangeably; in general, telehealth includes clinical and non-clinical services (medical education, administration, and research) and telemedicine includes only clinical services. Telemedicine generally refers to the transmission of medical information via telephone, the Internet or other networks for the purpose of consulting, and sometimes remote medical diagnosis, treatment and procedures.

The use of telemedicine for training healthcare providers on HIV/STIs has been extensively used in developed countries<sup>98</sup> and is increasingly being used in developing countries.<sup>87,96,99</sup> To conduct real time consultations, telemedicine more frequently

consists of using innovative technology such as satellite technology and video-conferencing devices.

Telemedicine is important to improve care delivery in remote areas, especially where there are geographical barriers.<sup>98</sup> Telemedicine has increased access to care for remote populations using Internet, cell phones, or other network systems, and reduced access problems related to distance.<sup>100</sup> Although its use is limited in developing countries, telemedicine may support access to medical consultation for rural areas.

In rural areas, telemedicine may support access for teleconsultation. For example, TeleMedMail, written in Java, is a software application to facilitate store-and-forward telemedicine by secure e-mail of images from digital cameras.<sup>101</sup> However, none of the telemedicine and e-health systems used in developed countries are ready to be deployed across a developing country as a whole.<sup>102</sup>

HOPE program is a collaborative initiative including healthcare professionals in the United States, Europe, Africa, Asia, and the Caribbean.<sup>103</sup> This program uses an Internet-conferencing technology to conduct interactive case conferences with healthcare professionals throughout the world.<sup>103</sup> This technology has been shown to be a feasible, cheap, and effective model for providing clinical support, consultative advice and continuing training and education to healthcare workers dealing with HIV-infected patients in resource-poor countries.

The Institute of Tropical Medicine, Antwerp, has created a telemedicine system (<http://telemedicine.itg.be>) for healthcare workers working in resource-limited settings to train them in the use of ART and AIDS care delivery. Specialists offer expert advice to their colleagues through an HIV/AIDS discussion forum covering topics such as ART and the management of opportunistic infections.<sup>104</sup>

## ICT to Support Education and Professional Development for Healthcare Workers Treating HIV/STIs in Developing Countries

Continuing Education (CE) for healthcare workers is widely available in developed countries. Healthcare workers can participate in CE courses in order to stay updated on new evidence and practice their skills. The available traditional CE programs for health professionals have generally shown small impact on sustained improvement in knowledge, and a failure to translate improvements in knowledge into improved healthcare provider practices or improved patient outcomes.<sup>105–107</sup> In many developing countries, CE programs have additional limitations. CE is provided largely in major urban settings and not easily accessible to most healthcare providers.<sup>108–110</sup>

Technology is playing a growing role in CE. The use of computers, Internet, and other forms of technology provides the opportunity for self-directed and problem-based learning-elements lacking in traditional CE methods. In recent years many organizations have been using technologies to improve the training and upgrading skills of healthcare providers. Internet-based CE is

an alternative to traditional CE, and has increased exponentially in recent years. Technological advances on the Internet now allow inclusion of complex information on Web sites, interactive links (bulletin boards, chat rooms, instant messaging, and discussion), video, images, and sounds. Thus, it is feasible to illustrate real clinical situations and encourage realistic problem solving. From both a practical and a theoretical perspective, Internet-based CE offers certain advantages over traditional CE.<sup>110–114</sup> These advantages include real-time interactivity, flexibility (location and time), potential for reinforcement (since it is continuously available), adjustability to adult learning approaches, potential for standardized materials of high quality, potential low cost, links to other resources, and accessibility to providers outside major urban centers.

Many training centers from nongovernmental, public, and private organizations have created Internet-based training programs on HIV/STIs for healthcare workers.

The National Network of STD/HIV Prevention Training Centers (NNPTC) is a group of regional centers constituted by health departments and universities funded by CDC (Centers for Disease Control and Prevention). Some members of the NNPTC offer online training to healthcare providers working in developing countries ([http://depts.washington.edu/nnptc/online\\_training/index.html#chlamydiaeasebased](http://depts.washington.edu/nnptc/online_training/index.html#chlamydiaeasebased)).

Some examples of the novel applications of comprehensive Internet-based training using interactive cases included: the HIV web study, the STD Case Series, and the Chlamydia Case-based Training.

Organizations from developing countries are also developing initiatives to create Internet-based training programs. In China, the Chinese National AIDS Prevention and Control Center (<http://www.chinaids.org.cn/>) developed an HIV/STI training course.<sup>115</sup> In Peru, the Universidad Peruana Cayetano Heredia has created an interactive course “STD/Serie de Casos” (<http://www.proyectopreven.org>) in Spanish using clinical cases to train healthcare providers from different regions for syndromic management of sexually transmitted diseases.<sup>116</sup>

## COMPUTER-BASED TRAINING ON HIV/AIDS

Computer-based training (CBT) is a method of training that uses computers. Participants learn by executing special programs. CBT programs include high levels of interaction and simulated environments. CBT is often delivered via CD-ROM. Many institutions are working to develop CBT programs for healthcare workers in developing countries.<sup>117,118</sup>

The International Training and Education Center on HIV (I-TECH) (<http://www.go2itech.org>) works in 10 countries around the world (Botswana, Ethiopia, Guyana, Haiti, India, Malawi, Mozambique, Namibia, South Africa, Tanzania). I-TECH has created training programs and developed a wide variety of media products. CD-ROMs and websites containing videos in multiple languages and training toolkits offer resources for developing, delivering, and evaluating training on HIV-related topics.

The WHO Reproductive Health Library (RHL) (<http://www.who.int/hrp/rhl/>), an electronic review journal published by the Department of Reproductive Health and Research at World Health Organization, compiled the best available evidence on sexual and reproductive health including HIV and STI and presents it as practical actions for clinicians and policy-makers. The information including training videos to help master clinical skills is distributed free through the RHL CD-ROMs to healthcare workers, primarily in under-resourced settings.

I-Med Exchange, International Association of Physicians in AIDS, created an Internet-based training program.<sup>119</sup> I-Med Exchange provides training to healthcare workers in 4 countries: South Africa, Lesotho, Swaziland, and Botswana.<sup>119</sup> The programs include presentations of clinical cases. Participants can access them via Internet or by using CD-ROMs. The program uses videos and chat rooms and offers the opportunity to ask questions of experts.<sup>119</sup>

## Access to Information

The Internet now allows healthcare workers to access the latest relevant information from journals without the need of paper based journal subscriptions or library access. Although universal access to information for health professionals is a prerequisite for meeting the Millennium Development Goals and achieving Health for All,<sup>120</sup> lack of access to information remains a major barrier in developing countries.<sup>121,122</sup> Despite this limitation, there are many successful initiatives in developing countries that might be expanded and replicated.

The WHO Sexually Transmitted Diseases Diagnostic Initiative<sup>123</sup> ([http://www.who.int/std\\_diagnostics](http://www.who.int/std_diagnostics)) publishes summaries and reviews related to new developments in laboratory and field diagnosis of STIs providing key information to healthcare providers around the world, particularly to those from developing countries.

BIREME (<http://www.bireme.org>), the Latin American and Caribbean Centre for Health Sciences Information, founded by an agreement between the Pan American Health Organization (PAHO)/WHO and the Brazilian Government. BIREME created SciELO (the Scientific Electronic Library Online) (<http://www.scielo.org>) the first and largest data based of free full-text access to health research information. BIREME created LILACS (<http://lilacs.bvsalud.org>), which indexes journals from Latin America and the Caribbean. BIREME also created the Virtual Health Library (<http://www.bvsalud.org>), which provides free online access to evidence-based resources that support healthcare decisions.

EMRO, World Health Organization Eastern Mediterranean Regional Office, created a database of books and journals from the region and created the EMRO Index Medicus that index more than 310 journals in the region. It is published in print, CD-ROM, and on the Internet.

The Association for Health Information and Libraries in Africa (<http://www.ahila.org>) and the African Index Medicus (<http://indexmedicus.afro.who.int/>) are other interesting initiatives.

Health InterNetwork Access to Research Initiative (HINARI) (<http://www.who.int/hinari/>), a WHO initiative, provides free access to approximately 2,300 online journals.

## Conclusion

The information and communication technologies (ICT) reviewed in this chapter provide people with different choices that can be applied in different patients to support HIV and STI prevention and care. Although ICT are being used for the prevention and control of HIV and STI, there are still several applications, such as the combined use of Internet and cell phones or the use of instant messaging systems, whose effectiveness in increasing HIV testing needs remains to be studied. Much less have been done in the use of ICT for prevention and care in other STIs. ICT have become ubiquitous even in resource-constrained settings, thus more research in their use for the prevention, control and treatment of HIV and STI in those countries needs to be conducted. While a variety of information and communication technology tools are in various stages of use for HIV/STI prevention, relatively few areas have accumulated a critical mass of evidence about effectiveness and sustainability. However, some of that evidence is compelling, and the potential for future uses appears large. Application to some areas of practice and research are nascent and evaluation of these tools would benefit from rigorous methodological designs.

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### Summary

This chapter starts by describing two applications that we consider have the most potential to support HIV and sexually transmitted infections (STI) care in developing countries: mobile devices and the Internet. Then we describe some notable examples of information systems used for clinical care in developing countries. Finally, we present how information and communication technologies (ICT) are supporting education and professional development for healthcare workers treating HIV/STI in developing countries.

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# 15

## Vaccines for Sexually Transmissible Infections

Anna McNulty

### Introduction

Vaccines play a special role in the health and security of nations. The World Health Organization (WHO) cites immunization and the provision of clean water as the two public health interventions that have had the greatest impact on the world's health, and the World Bank notes that vaccines are among the most cost-effective health interventions available. Over the past century, the integration of immunization into routine healthcare services in many countries has provided caregivers with some degree of control over disease-related morbidity and mortality, especially among infants and children.

The terms *vaccination* and *immunization* are often used interchangeably, although technically the former denotes the administration of a vaccine, whereas the latter refers to the induction or provision of immunity by any means, active or passive. Thus, vaccination does not guarantee immunization, and immunization may not involve vaccine.

Because the immune response is genetically controlled, all individuals cannot be expected to respond identically to the same vaccine. Additional vaccine constituents (adjuvants) affect immunogenicity, efficacy, and safety and may render one formulation superior to another formulation of the same antigens.

### Approaches to Active Immunization

The two standard approaches to active immunization are (i) the use of live, generally attenuated infectious agents (e.g., measles virus); and (ii) the use of inactivated agents (e.g., influenza virus), their constituents (e.g., *Bordetella pertussis*), or their products, which are now commonly obtainable through genetic engineering (e.g., hepatitis B vaccine). For many diseases (e.g., poliomyelitis), both live and inactivated vaccines have been employed, each offering advantages and disadvantages.

Live attenuated vaccines consisting of selected or genetically altered organisms that are avirulent or dramatically attenuated, yet remain immunogenic, typically generate long-lasting immunity. These vaccines are designed to cause a subclinical or mild illness

and an immune response that mimics natural infection. They offer the advantage of microbial replication *in vivo*, which simulates natural infection; they may confer lifelong protection with one dose; they can present all potential antigens, including those made only *in vivo*, thus overcoming immunogenetic restrictions in some hosts; and they can reach the local sites most relevant to the induction of protective immunity.

Nonliving vaccines typically require multiple doses and periodic boosters for the maintenance of immunity. The exceptions to this rule are the pure polysaccharide vaccines, whose effects cannot be boosted by additional exposures because polysaccharides do not elicit immunologic memory. Nonliving vaccines administered parenterally fail to induce mucosal immunity because they lack a delivery system that can effectively transport them to local mucosal antigen-processing cells. Despite their many advantages, live vaccines are not always preferable. STIs are most likely to infect via the mucosa in the majority of exposed people. It therefore seems logical to develop vaccines that are designed to be administered via the mucosa or to stimulate mucosal immunity to prevent or combat these infections.<sup>1</sup>

### POSTEXPOSURE IMMUNIZATION

For certain infections, active or passive immunization soon after exposure can prevent or attenuate disease expression. For example, giving either measles immune globulin within 6 days of exposure or measles vaccine within the first few days after exposure may prevent symptomatic infection. Proper immunization for tetanus plays an important role in dirty-wound management. The need for active immunization—with or without passive immunization—depends on the wound's condition and the patient's immunization history. Similarly, for persons who have not been actively immunized, administration of hepatitis A immune globulin within 2 weeks of exposure to hepatitis A virus is likely to prevent clinical illness. Evidence also supports the efficacy of human hepatitis B immune globulin in preventing disease after exposure.

## Vaccines for Sexually Transmitted Infections

Vaccination is potentially one of the most effective strategies to reduce the incidence of STIs. In general for vaccination as a strategy to be successful at a population level, the vaccine must be safe, effective, and accessible, resulting in high levels of coverage.

There are, however, differences between vaccination strategies that will be effective for childhood infections versus STIs. Firstly, the risk of acquiring an STI is limited to the sexually active population and it is generally women who suffer complications of infection. In addition the risks of acquiring and transmitting an STI are extremely variable across the population whereas this is not the case for childhood infections.<sup>2</sup> Thus, it is possible that vaccines with only partial efficacy or only vaccinating one sex, for example human papillomavirus (HPV) vaccination, will be effective strategies.

### Barriers to Vaccine Uptake

In general terms, barriers to vaccination center around health beliefs and health behaviors. These include perceived susceptibility to the disease, concerns regarding the perceived benefits and efficacy of vaccination, and beliefs about disease severity. In addition with the increasing number of infant vaccinations now recommended in many jurisdictions, the complexity of the vaccine schedule can be a barrier to both vaccine uptake and completion.<sup>3</sup>

In resource poor settings cost is the major barrier to vaccine implementation. The Global Alliance for Vaccines and Immunization (GAVI) is a successful partnership between public and private stakeholders established in 2000 with the aim of increasing the availability of vaccines through innovative financing in 72 of the world's poorest countries. The WHO's Expanded Program on Immunization (EPI) led to the concept of integrating maternal and child health with immunization programs. When done successfully between compatible programs, this has resulted in less duplication of services and competition for resources.<sup>4</sup>

One of the specific barriers with regard to vaccines against STIs is a seeming endorsement of a decline in sexual moral values. This argument has been applied in the implementation of the HPV vaccination in adolescent girls in a number of countries. However, available data suggest sexual risk does not increase as a result of vaccination.<sup>5</sup> In many countries the HPV vaccine has been marketed as a vaccine to protect against cervical cancer with little mention made of sexual transmission of HPV.

Vaccine acceptance has been shown to be influenced by the attitude of the healthcare provider and the patient's perception of this attitude. Thus, an important component in the development of health promotion campaigns for STI vaccines is education of healthcare providers.<sup>3</sup>

### Strategies for Vaccine Development

The important factors which must be considered when determining the feasibility of developing a vaccine are:

- the nature of the organism (its complexity),

- the nature of the infection (acute or chronic),
- the host's ability to develop natural immunity after infection,
- whether the organism is cultivatable,
- the degree of antigenic diversity, and
- the availability of a suitable animal model.

In analyzing these factors, it would appear that most STI pathogens are structurally complex and confer limited, if any, immunity following infection. Many of these pathogens show significant antigenic diversity, which enables the pathogen to avoid the host's immune system, and may be a major obstacle in vaccine development. Because humans are the only natural host for most STI pathogens, it has been difficult to find an animal model that adequately imitates all aspects of the human disease. However, except for *T. pallidum* and HPV, all STI pathogens are cultivatable, which gives us a reason for hope in the challenging task of developing vaccines against STI pathogens.

### Potential Vaccination Strategies

The fact that the classic STI agents are pathogenic only in humans favors their eradication. However, the tendency of certain STI pathogens (gonococcus, chlamydia, HSV) to cause subclinical or asymptomatic infection in some individuals indicates that these organisms can effectively avoid the host immune system.

For successful implementation of any vaccination strategy the target population must be carefully defined and its easy accessibility assured.

Different STIs may require different vaccine strategies. For eradication or elimination, universal vaccination is required (with a vaccine that provides lifelong immunity), which is usually administered during infancy or childhood. However, this is an expensive strategy and might not be widely accepted. Containment could probably be accomplished by selective immunization of high-risk population (adults in sexually active years).

An alternative strategy would be selective vaccination, i.e., a vaccine that would be effective in only males or females. Immunization of one would probably, as a result, prevent infection in the other. A disadvantage of selective vaccination is that it is often difficult to identify or access groups most at risk and ensure adequate coverage of vaccine. However, a selective STI vaccination strategy could mimic strategies being considered for HIV vaccination in developing countries. These strategies include targeting urban adolescents and young adults (10–19 year old) attending school, and women of childbearing age accessed by WHO Expanded Program on Immunization (EPI) to receive the tetanus toxoid.<sup>4</sup> A strategy to accomplish maximum coverage should focus at two different goals: (i) containment, by targeting adults in the sexually active period (most likely 15–49 year old, with priority to 15–25 years of age) to ensure rapid “mopping up” of those people at risk of infection; while (ii) aiming at elimination by ensuring integration of vaccination into existing programs, such as EPI, and school immunization programs to replace the “mopping up strategy” once those immunized at young ages reach sexual activity.



## Hepatitis B Vaccine

Hepatitis B vaccination is highly effective in preventing both hepatitis B and D. Recombinant hepatitis B vaccine has now replaced the use of plasma derived vaccines. It is available in adult and child formulations and in combination with hepatitis A vaccine. It is also available as part of a polyvalent vaccine for infant immunization.

### EFFECTIVENESS IN CLINICAL TRIALS

The original plasma derived hepatitis B vaccine was demonstrated to be effective in high-risk men studied in 2 large randomized blinded placebo controlled studies in the United States in the late 1970s. Participants in these studies received doses of either 20 or 40 µg at 0, 1, and 6 months and after the third dose more than 95% of recipients had anti-HBs titers  $\geq 10$  IU/L.<sup>6</sup>

A third-generation hepatitis B vaccine containing pre S1 and pre S2 has been developed and trialled. Vaccines containing pre S1 and pre S2 are thought to stimulate a more robust immune response, particularly important for poor and non responders to the currently commercially available vaccines.<sup>4,7</sup>

### EFFECT AT REDUCING DISEASE BURDEN

A Cochrane review of hepatitis B vaccination in those not previously exposed or of unknown exposure status reviewed 12 studies that met their inclusion criteria.<sup>9</sup> Most of the studies were of poor quality. In four of these studies, Hepatitis B vaccination reduced the risk of developing Hepatitis B surface antigen by 88% and for hepatitis B core antibody by 62% when compared with no vaccination. Previous Cochrane reviews have shown benefit of hepatitis B vaccination in high-risk groups such as healthcare workers and in infants born to mothers with chronic hepatitis B.

### LOW ENDEMICITY (<2% POPULATION HBsAg POSITIVE)

The WHO recommends universal infant vaccination in this population as the most effective method of reducing hepatitis B prevalence.<sup>10</sup> In low-prevalence countries a significant proportion of chronic infection is acquired via childhood transmission. Selective screening of mothers, and vaccination of at-risk infants, may miss a significant proportion of those at risk, as those most likely to be infected with hepatitis B may be those most likely to have minimal or no antenatal care.

### MODERATE ENDEMICITY ( $\geq 2$ – $< 8$ % POPULATION HBsAg POSITIVE)

Universal infant vaccination is recommended in countries with a moderate prevalence of hepatitis B. The benefits of this approach have been demonstrated in a number of different countries. In Gambia, following the introduction of universal infant vaccination, the rate of chronic HBsAg carriage decreased from 10.3% to 0.6%. Similar decreases have been noted in Alaska, Italy, China, Thailand, and Saudi Arabia.

### HIGH ENDEMICITY ( $\geq 8$ % POPULATION HBsAg POSITIVE)

Universal infant vaccination commenced in Taiwan in 1987 with a catch up program for children and adolescents introduced over subsequent years. Over 90% of infants complete the vaccination course and numerous studies have demonstrated a dramatic impact on hepatitis B epidemiology in Taiwan. In addition to decreasing the rate of HBsAg carriage in those under 15 years of age from 9.8% to 0.7% in 1999, there has been a 75% decrease in the incidence of hepatocellular carcinoma in children 6–9 years old since the national vaccination program began.<sup>11</sup>

A significant benefit has already been seen within 20 years of the introduction of universal infant vaccination and this will increase as the vaccinated cohort ages.

### COST EFFECTIVENESS

Cost effectiveness of hepatitis B vaccination increases with the use of combination polyvalent vaccines from the infant/childhood vaccination schedule which incorporate hepatitis B. Combination polyvalent vaccines are often the same price or cheaper than monovalent vaccines.<sup>12</sup>

### HIGH, MODERATE, AND LOW ENDEMICITY COUNTRIES

Universal infant vaccination is cost effective.<sup>13</sup>

### VERY LOW ENDEMICITY COUNTRIES ( $\leq 0.5$ % POPULATION HBsAg POSITIVE)

Cost effectiveness studies in this setting have produced contradictory results depending on the type of evaluation conducted. The ability to achieve sufficient coverage with selective vaccination needs to be assessed, however, if high, this strategy is currently considered more cost effective than universal infant vaccination.

### HEPATITIS B VACCINATION IN HIV POSITIVE INDIVIDUALS

A number of different studies have reported lower efficacy of hepatitis B vaccination in HIV positive individuals with between 17.5 and 62% developing a protective antibody response even in the era of highly active antiretroviral therapy.<sup>14</sup> Those less likely to respond have a lower nadir CD4 count than those who do respond. Conversely, those with undetectable HIV RNA are more likely to respond to hepatitis B vaccination. In those who are HIV positive, hepatitis B surface antibody levels are lower than in HIV negative individuals and decline more quickly. For this reason a number of guidelines recommend using hepatitis B vaccine at twice the dose recommended for immunocompetent individuals and to check hepatitis B surface antibody levels annually.

In those who fail to respond to the initial course of vaccination, a repeat course will result in seroconversion in up to 51%.<sup>14</sup>

## Hepatitis A Vaccine

Vaccination against hepatitis A has been available since 1994. There are currently 5 hepatitis A vaccines available internationally. Three of these are live attenuated vaccines. A virosomal hepatitis A vaccine has also been developed and trialled but is not widely available. Vaccines are licensed for both adults and children and there is also a combined hepatitis A and B vaccine.

### EFFECTIVENESS IN CLINICAL TRIALS

Immunization following a 2 dose schedule at 0 and 6 months produces neutralizing antibodies which protect against both infection and disease. Clinical effectiveness has only been studied in children, however it is reasonable to assume that adults would develop similar protective levels of immunity.

More than 88% of adults and children acquire a protective antibody level within 2 weeks of the first injection and 99% at 1 month following the first injection. One month after the second dose 100% had protective immunity.<sup>15,16</sup>

### EFFECT AT REDUCING DISEASE BURDEN

In areas of high endemicity the impact on clinical disease burden is small as most infection prevented is asymptomatic childhood disease. In countries of moderate and low endemicity the impact is greater as adult disease is more likely to be symptomatic. The introduction of universal infant hepatitis vaccine in high-incidence areas in the US and in Israel led to a rapid reduction in disease incidence in both children and adults reflecting the impact of herd immunity.<sup>7</sup>

Targeted hepatitis A vaccination is effective at reducing disease burden when given in “closed communities” due to both individual and herd immunity. Hepatitis A vaccination postexposure has also proven effective during hepatitis A outbreaks.

### COST EFFECTIVENESS

In considering the introduction of large scale vaccination programs the public health impact of hepatitis A needs to be weighed up against that of other vaccine preventable diseases.

### HIGH ENDEMICITY

In the generally resource poor countries, hepatitis A acquisition in childhood is almost universal and generally asymptomatic. Consequently hepatitis A is a minor public health issue and large scale immunization efforts are not recommended.<sup>16</sup>

### MODERATE ENDEMICITY

Universal infant vaccination is most likely to be cost effective in such countries however, costs associated with hepatitis A infection and a hepatitis A vaccination vary widely making generalizability of study findings difficult.<sup>17</sup> A number of countries

(for example, Israel, USA, Italy, Chile) have introduced universal infant vaccination and found it to be cost effective particularly in high-incidence areas within the country. Cost effectiveness is increased when a combined hepatitis A/hepatitis B vaccine is used.<sup>17</sup>

### LOW ENDEMICITY

A number of economic evaluations have looked at targeted vaccination and in most of these studies this approach is not cost effective. Vaccination of travelers to moderate or high endemicity countries is recommended.<sup>16</sup> The cost effectiveness of screening and vaccinating men who have sex with men (MSM) is unknown, however, one US study argued that replacing hepatitis B vaccination with hepatitis A and B in all STD clinic patients was cost-effective.<sup>18</sup>

## Human Papillomavirus Vaccine

There are currently 2 licensed prophylactic HPV vaccines. Both vaccines use virus like particles (VLPs) of the recombinant major capsid (L1) protein of HPV to stimulate a protective immune response to the relevant HPV types. Since the VLPs contain no viral DNA they cannot infect cells or reproduce. Gardasil is a quadrivalent vaccine (Merck and Co, Inc) and induces a protective response against HPV types 16,18, 6,11 while Cervarix (GlaxoSmithKline) is a bivalent vaccine against types 16,18. HPV types 16, 18 are responsible for ~70 % of cervical cancers worldwide and HPV 6,11 are responsible for ~90% of genital warts. Both vaccines are highly immunogenic and stimulate higher antibody levels than those seen after the clearance of natural HPV infection. Both vaccines have a 3 dose schedule over 6 months and require storage at 2–8°C. Studies in adolescent boys 9–15 years of age have demonstrated antibody responses similar to those found in adolescent girls.<sup>19</sup>

### EFFECTIVENESS IN CLINICAL TRIALS

Clinical trials in women have demonstrated more than 90% efficacy in the prevention of infection, persistent infection and high-grade cervical lesions in those who adhered to the trial protocols (Table 15.1).<sup>20</sup> Follow-up data are available for at least 6 years in some cohorts. The quadrivalent vaccine also protected against external genital warts and vulval (VIN) and vaginal (VaIN) intraepithelial neoplasia.<sup>21</sup> Entry into the clinical trials was restricted by age, number of sexual partners, and pre-existing history of cervical abnormalities.

Clinical trials have shown that the vaccine is effective in men. A study of 4065 men aged 16–26 years in a randomized placebo controlled trial demonstrated vaccine efficacy against any HPV 6/11/16/18 external genital lesion (EGL) of 90.4% and against persistent infection of 85.6%.<sup>22</sup> A smaller study in 602 MSM demonstrated vaccine efficacy of 79% and 94.4% against any HPV 6/11/16/18 EGL and persistent infection, respectively.<sup>23</sup>

**Table 15.1:** Summary of Clinical Trial Effectiveness, Population Level Impact and Cost Effectiveness of Currently Available STI Vaccines

Clinical trials	Hepatitis B	Hepatitis A	Human papilloma virus
	Highly effective	Highly effective	Highly effective (adolescent girls and young women <26 years)
Population level impact	Universal infant vaccination effective in all settings	<b>Low/moderate endemicity:</b> Effective at reducing disease incidence <b>High endemicity:</b> Less impact if infection acquired predominantly in childhood	Anticipated to have maximal impact in countries with inadequate or no cervical screening programs
Cost effectiveness	Highly cost-effective in all settings	<b>Low endemicity:</b> Depends on risk <b>Moderate endemicity:</b> Universal childhood vaccination cost-effective <b>High endemicity:</b> Unlikely	<b>Women:</b> Anticipated to be cost-effective especially if increased age at first cervical screen and/or increased screening interval <b>Men:</b> Insufficient data

Other populations to be studied include infants and immune compromised individuals.

Work is ongoing to monitor the duration of protective immunity, examine alternative vaccination schedules and monitor the safety profile of the vaccines. The impact of HPV vaccination on cervical screening programs is being examined in various countries.

### EFFECT AT REDUCING DISEASE BURDEN

In resource poor countries where the incidence of cervical cancer is higher due to a lack of, or inadequate cervical screening programs, the impact of HPV vaccines will be greater. There is evidence that both vaccines<sup>24</sup> offer partial protection against genetically related oncogenic nonvaccine HPV types 31/33/45/52/58. Cervical intraepithelial neoplasia (CIN) 1-3 and adenocarcinoma *in situ* due to these types was reduced by 43.6% following vaccination with the quadrivalent vaccine in women without pre-existing infection with these HPV types.<sup>25</sup> Cross protection against these nonvaccine oncogenic HPV types that may be responsible for up to 20% of cervical cancers will add further to the anticipated reduced incidence of cervical cancer. Programs for vaccine implementation in resource poor countries are currently being developed.<sup>26</sup>

In those countries that elect to use the quadrivalent vaccine there will be a significant reduction in healthcare utilization for the management of external genital warts, however, it is too early to quantify the impact on a large scale. Early evidence of benefit exists in Australia where government funded quadrivalent HPV vaccination for 11–12-year-old girls and a catch up program for girls and women up to 26 years of age commenced in April 2007. A study at Melbourne Sexual Health Centre showed a decrease in genital wart diagnoses in new patients (heterosexual women <28 year old and heterosexual men) when comparing the years 2004–7 and 2008 suggesting that comprehensive vaccination of females can produce early benefits in both women and heterosexual men.<sup>27</sup>

The licensed HPV vaccines have no impact on natural history or clinical disease in those who have already acquired the vaccine HPV type prior to vaccination.<sup>28</sup> However, some tantalizing

early work has been done utilizing a different type of HPV vaccine for therapeutic purposes. In a study by Kenter et al.<sup>29</sup> the immunogenicity and efficacy of a vaccine containing HPV-16 E6 peptides and 4 HPV-16 E7 synthetic peptides in the treatment of grade 3 vulvar intraepithelial neoplasia was examined. Of the 20 women treated, 15 of 19 had a clinical response at 12 months of follow-up and 9 of 19 had complete remission at 12 months of follow-up. Clinical response was associated with a stronger vaccine induced T cell response.

### HPV VACCINE RECOMMENDATIONS

The HPV vaccine is routinely recommended for 11 and 12 year-old girls. The vaccine series can be started at 9 years of age. Catch-up vaccination is recommended for 13 through 26 year old females who have not yet received or completed the vaccine series.

Ideally, females should be vaccinated before onset of sexual activity, when they may be exposed to HPV. However, sexually active females may also benefit from vaccination since few young women are infected with all HPV types targeted by the vaccine. Females who already have been infected with one or more HPV types would still get protection from the vaccine types they have not acquired. Currently, there is no test available for clinical use to determine whether a female has had any or all of the HPV types targeted by the vaccine.

#### The HPV vaccine can be given to females who:

- are lactating;
- have minor acute illnesses, such as diarrhea or mild upper respiratory tract infections, with or without fever;
- have an equivocal or abnormal Pap test, a positive Hybrid Capture II® high-risk test, or genital warts. However, women should be advised that data do not indicate that the vaccine will have any therapeutic effect on existing Pap test abnormalities, HPV infection or genital warts; and
- are immune compromised, either from disease or medication. However, the immune response to vaccination and vaccine efficacy might be less than in immune competent females.



**The HPV vaccine should not be given to females who:**

- are pregnant. Although the vaccine has not been causally associated with adverse pregnancy outcomes or adverse effects on the developing fetus. However, data on vaccination in pregnancy are limited;
- have a history of immediate hypersensitivity to yeast or to any vaccine component; and
- have moderate or severe acute illnesses. In these cases, girls/women should wait until the illness improves before getting vaccinated.

**HPV VACCINE ADMINISTRATION**

The vaccine should be delivered through a series of three intramuscular injections over a 6-month period. The second and third doses should be given 2 and 6 months after the first dose. The vaccine can be administered at the same visit as other age-appropriate vaccines.

**COST EFFECTIVENESS**

A number of modeling studies in developed countries have demonstrated cost effectiveness when all adolescent girls are vaccinated particularly if this leads to an increase in the age when cervical screening commences and/or a reduction in the frequency of cervical screening.<sup>30</sup>

In resource poor countries, the cost of the vaccine will be the major determinant of cost effectiveness. Global agencies purchasing large vaccine volumes have the ability to negotiate lower prices, however, individual countries will still need to consider program costs in the light of competing health priorities. In addition, since the vaccine is administered in preadolescents, program costs will be higher as resource poor countries in general, do not have specific health programs for this age group. A number of demonstration projects are being implemented in resource poor settings to examine different models of vaccine delivery.

There are currently insufficient data on the cost effectiveness of vaccinating men. However, mathematical modeling suggests that with high coverage rates in women there is little additional benefit in vaccinating men in order to prevent cervical cancer in women. The direct cancer prevention effects in men would be lower than in women due to the lower incidence of HPV related cancers in men.

**Herpes Simplex Virus Vaccine**

The prospect for developing a vaccine against HSV-2 that could provide sterilizing immunity is thought to be unrealistic. The goals of the vaccines under development are rather to prevent the establishment of latent infection by blocking access of the virus to sensory ganglia, to reduce the severity of the symptoms, and/or to reduce the frequency of recurrences. There has been more significant progress in the development of a vaccine against herpes simplex virus type 2 (HSV-2) infection. A HSV-2 glycoprotein D subunit vaccine developed by GlaxoSmithKline (GSK) proved effective only in women who were seronegative for both HSV-1

and 2 at baseline.<sup>31</sup> It was not effective in men. The subset of women in whom the vaccine was effective experienced a 73% reduction in genital herpes disease compared with controls.<sup>31</sup> A further study to examine the impact of this vaccine in more than 8000 women was recently terminated when no effect was found.<sup>32</sup> Studies of HSV vaccine effectiveness need to distinguish between protection against disease and protection against infection. An HSV-2 vaccine that prevents disease but not infection will need to reduce transmissibility through a reduction in viral shedding to be effective at a population level.<sup>33</sup>

A novel, live attenuated HSV-2 candidate vaccine has been developed by Xenova/GSK using a replication-impaired virus mutant that lack the gene of the essential glycoprotein gH (ICP8 gene mutation) as a disabled infectious single cycle (DISC) virus vaccine. The vaccine was tested in phase II trials in the USA as a therapeutic vaccine in HSV-2 seropositive symptomatic patients. It was well-tolerated and induced neutralizing antibodies and cytotoxic T lymphocytes (CTL) in 83% of the vaccinees, but no difference in time to recurrence and no difference in virus shedding were observed as compared with controls. The development of the DISC vaccine has been refocused toward its use as a prophylactic vaccine.

- Another live, replication-impaired vaccine is currently under development by Avant Immunotherapeutics. Other viral mutants that are defective for replication and impaired for establishment of latency, such as mutant dl5–29, are at a preclinical stage of development.
- A live attenuated vaccine based on a replication-competent ICP10 mutant of HSV-2 developed by AuRix is in phase II clinical study.

For the developing world where the acquisition of HSV-1 in childhood is almost universal, a vaccine that is effective only in those seronegative to HSV-1 and 2 would be of minimal benefit. Work is continuing on the development of alternative models for an HSV vaccine.

**Vaccines Against other STIs**

There has been little progress in the development of vaccines against the bacterial pathogens *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Treponema pallidum*, *Haemophilus ducreyi*, and *Klebsiella granulomatis*. Work is ongoing to understand the biology, pathogenesis and immune responses to these organisms in both animal models and humans.

**CHLAMYDIA TRACHOMATIS**

A safe vaccine administered prior to adolescence that is effective through childbearing age would have a significant impact on the spread of the disease. The lack of a suitable animal model and the difficulties in genetic manipulation of the bacterium has hampered progress in the field. The vaccine that has been tried is a subunit vaccine (TRACVAX) which has been tested in a randomized phase I trial designed to assess the safety and



immunogenicity of the candidate vaccine and a surface-exposed antigen termed polymorphic membrane protein D (PmpD) which induces neutralizing antibodies *in vitro* in animal models.

Identification of potential vaccine antigens is today an active area of research which is greatly helped by the availability of the complete *C. trachomatis* genome sequence, allowing for the identification and testing of candidate proteins based on their similarity to proteins important in protective immunity against other bacterial pathogens.

## NEISSERIA GONORRHOEAE

The lack of a suitable animal model and the considerable antigenic variability of the bacterium have hampered the development of a vaccine for gonorrheal disease. Attachment of gonococci to mucosal cells is mediated in part by the pili, and it was found that rabbit antibody to pili reduces attachment of the bacteria to mammalian cells. Pilin was therefore chosen as the most likely vaccine candidate and tested for efficacy in military recruits and in volunteers challenged urethrally. This approach was met with some success, but protection was strain-limited, due to the high rates of antigenic variation of pili. Porin also was studied as a vaccine antigen but the induced anti-porin antibodies were not bactericidal.

## HIV Vaccines

The development of a safe and effective vaccine is hampered by the high genetic variability of HIV, the lack of knowledge of immune correlates of protection, the absence of relevant and predictive animal models, and the complexity of the implementation of efficacy trials, especially in developing countries. The first phase I trial of an HIV vaccine was conducted in the USA in 1987. Since then, more than 30 candidate vaccines have been tested in over 80 phase I/II clinical trials, involving more than 10,000 healthy human volunteers. Two phase III trials have been carried to completion and a third one is in progress. The different vaccine types that have been used are:

- live attenuated vaccines,
- subunit vaccines, and
- live recombinant vaccines.

## OTHER VACCINAL APPROACHES

Induction of persistent HIV gag-specific CD8<sup>+</sup> CTL responses was attempted in a trial involving immunization with a fusion protein comprising the HIV p24gag protein and detoxified *Bacillus anthracis* lethal factor. Multiepitopic combinations of peptides, fusion proteins, and long lipopeptides also are at an early stage of clinical development, either alone or in prime-boost combinations with live vector-based recombinant vaccines. Some of these candidate vaccines will be tested as therapeutic vaccines in patients as a complement to antiretroviral therapy. tat has been shown to act as a viral toxin and to promote apoptosis of uninfected bystander T-cells and secretion of Th2 cytokines.

The population-wide effects of partially effective vaccines that do not prevent infection but only can reduce viral loads are largely unknown. Mathematical models predict that the factor with the greatest impact on reducing infections and deaths will be the degree of viral load reduction. A 90% reduction in viral load, which is a reasonable expectation with current candidate vaccines under development, would significantly reduce HIV mortality within 20 years after introduction of the vaccine.

The development of a safe, effective, and affordable HIV vaccine remains a formidable scientific and public health challenge at the dawn of this century.

## Conclusion

STIs remain an important and costly public health problem worldwide. Owing to the serious morbidity and sequelae, priorities for vaccine development should be focused on gonorrhea, chlamydia, and syphilis. However, there has been relatively little progress particularly with vaccine development for gonorrhea and syphilis, and significantly more work is required in chlamydia vaccine development. The problem of stimulating long-term immunity in the genital tract is still a challenge as little is known about genital tract immunology. Vaccination against STIs is one component of an effective STI/HIV prevention program. Focus on STI screening, treatment and behavioral change to reduce the risk of HIV transmission remain key components of an effective response. Work should continue in the search for effective vaccines against other STIs of public health significance.

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## Introduction

There is no vaccine for HIV. Developing a safe and effective HIV vaccine is one of the defining scientific challenges of our times. Two (*gp120* proteins and adenovirus vector trials) approaches tested so far in large-scale human efficacy trials have failed and a third (canarypox vector plus *gp120* protein) showed only marginal efficacy. Novel vaccine approaches are currently in preclinical and early stage clinical trials, although there is no consensus on what an eventually successful approach will comprise. Although the challenges in developing an HIV vaccine are daunting, the global research effort surrounding HIV vaccine development is intense. This chapter examines (*i*) why HIV is such a difficult vaccine target, (*ii*) what immune responses may be helpful in protecting against HIV, (*iii*) the results of efficacy HIV vaccine trials to date, (*iv*) novel approaches in the pipeline, and (*v*) logistical issues surrounding the development of an HIV vaccine.

## Roadblocks to HIV Vaccine Development

### HIV STRAIN VARIABILITY

There are an enormous number of HIV variants, dwarfing issues of strain variability in other pathogens such as influenza. The substantial rate of viral replication, a highly error prone reverse transcriptase and significant rates of recombination between variants combine to generate a vast number of strains, even within a single individual.<sup>1,2</sup> This variation is compounded by the capacity of individual proteins to tolerate changes at numerous amino acid positions and retain still function.<sup>3,4</sup> Although most mutations result in defective virions, sufficient numbers of functional variants are generated capable of evading the gamut of humoral and cellular immune responses generated in each individual. The potential for new viral variants is highest during the acute phase of the infection when the availability of host cells, predominantly memory CD4 T cells, is highest. At a population level, this interplay between viral diversity and the host cell response manifests in the extensive sequence variation observed in the two most immunogenic proteins, *Env* and *Gag*, with 35% and 25% variation across subtypes, respectively.

How can a vaccine contend with such sequence variation? Many approaches utilize representative strains, those from an ancestral progenitor, or from “consensus” sequences that include the most common amino acid at each position. In either case, the intention is to include the best possible fit to the range of circulating sequences. In this scenario a vaccine sequence covering subtype C (the most common HIV subtype worldwide) will vary from circulating strains by a maximum of 8% for the most variable proteins, compared to the 20% variation that exists within the subtype.<sup>5</sup> Extending this principle to a group M vaccine, designed to cover all subtypes and circulating recombinant forms, variation from the vaccine sequence increases to 15%. An alternative approach is to rationalize antigen selection since responses to some HIV proteins are more effective than others.<sup>6</sup> Highly variable regions, such as Envelope are subject to escape with little cost to the virus and therefore are ineffective.<sup>7</sup> In comparison, structurally or functionally constrained proteins, such as *Gag* p24, are more conserved and escape, when it occurs, is often associated with impaired viral replication and reduced viral load.<sup>8–10</sup> However, it may be necessary to include additional less conserved sequences in vaccine antigens to maximize the breadth of the response.<sup>11–13</sup> The net effectiveness of vaccines that target sufficiently broad numbers of conserved HIV epitopes across the target population remains speculative.

### NEUTRALIZING ANTIBODY PROBLEM

Successful viral vaccines typically induce neutralizing antibody (NAb) that block most viral variants, but all current HIV vaccine candidates have failed to induce broadly reactive NAb. Monomeric *gp120* subunit vaccines induced antibody but were unable to neutralize HIV-1.<sup>14</sup> In HIV-infected individuals, NAbs are eventually produced but (*i*) typically only neutralize closely related strains and (*ii*) are soon rendered ineffective as a result of viral escape.<sup>15,16</sup> Inducing NAbs with broad reactivity to multiple strains is difficult for several reasons: (*i*) conserved epitopes in *Env* that are involved in binding to CD4 and the chemokine co-receptor are shielded by extensive glycosylation, (*ii*) the CD4 binding site is recessed and difficult to access by antibodies, and (*iii*) conserved

epitopes are exposed only briefly during conformational changes just prior to fusion with the host cell membrane. However, a limited number of broadly neutralizing antibodies have been identified in HIV-infected individuals and current vaccine development is focused on presenting these rare, neutralization epitopes.<sup>17</sup> Recent evidence does, however, suggest that low titer NAb can prevent exposure to low doses of simian and human immunodeficiency virus (SHIV) inoculation in macaques.<sup>18</sup>

### INTEGRATION AND LATENCY

HIV is a retrovirus and undergoes proviral integration into the host genome during the replication cycle. A proportion of HIV-infected cells, predominantly CD4 memory T cells, will become quiescent and harbor latent virus. Within these latently infected cells, virus production is absent and the HIV is effectively hidden from immune surveillance. A vaccine must therefore maintain sufficient circulating antibody to completely prevent infection or, in combination with cellular immune responses, limit infection to a small number of cells that can be destroyed. Failure to eliminate early infection will lead to an integrated viral reservoir and an established infection. Immune responses that target infected cells (such as CD8+ cytotoxic T cells) could still blunt the level of established infection leading to a delay in progression to AIDS; this has been observed in macaque-SIV studies and has now become a well-described secondary goal of HIV vaccines focussed on cellular immunity.

### LACK OF ROBUST SMALL ANIMAL MODEL

Attempts to develop robust rodent models of HIV that would allow ready investigation in simple animal facilities by many researchers have been marginally successful to date. Preclinical testing of vaccines is generally performed in nonhuman primate (NHP) models. Several species of Asian macaques have been shown to be susceptible to AIDS induced by simian immunodeficiency virus (SIV), a lentivirus closely related to HIV-1. A number of SIVs and chimeric SIV/HIV viruses have been used in various combinations to test vaccine prototypes. This is not an ideal situation for comparative evaluation of vaccine prototypes but will not be resolved until one model is validated by successful clinical trial evaluation. However, it is generally accepted that challenge with SIVmac239/251 or similar biological isolates best model HIV-1 infection. The models are also being fine tuned with regard to genetic predisposition to resistance, so that for example, MHC molecules that confer increased resistance to infection (e.g., Mamu-A\*01, Mamu-B\*17, Mane-A\*10) are controlled for in macaque studies. Certainly, which model is used for preclinical studies can demonstrably influence the outcome of a study and have implications for clinical development. This was highlighted in preclinical testing of the Merck Recombinant Ad5 vaccine, recently evaluated in a phase IIb proof of concept "STEP" trial. In preclinical testing, protection in rhesus macaques was demonstrated against the chimeric SHIV89.6P virus (which uses CXCR4 as an entry coreceptor and is more readily neutralized) but not against SIVmac239 (which uses CCR5 and is difficult to neutralize). In this case, clinical evaluation was better predicted by the SIVmac challenge.

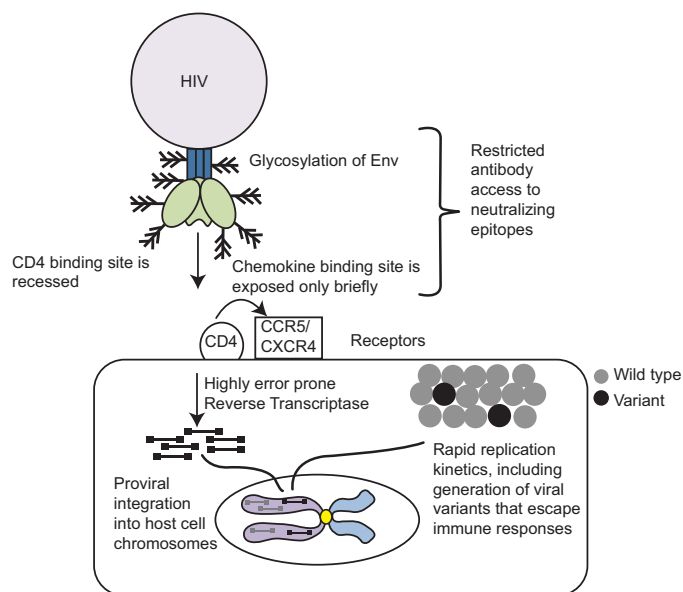
### MUCOSAL IMMUNITY

Vaccines for HIV must also act at sites of HIV entry and early replication. HIV infections are most commonly transmitted via genital epithelia, and the acute phase of infection occurs primarily in the intestinal mucosa. Vaccines administered via a mucosal route (e.g., intranasal) typically induce responses at genital mucosal sites. Successful responses induced by HIV vaccines will likely need to be activated very quickly (within hours to days) at the site of entry to limit and potentially clear the virus at the initial site of infection.<sup>19,20</sup> The most effective vaccines tested to date in macaques are live attenuated SIV strains that in many cases are capable of controlling viral replication to below the level of detection. This protection is in part mediated by CD8 T cells acting quickly at mucosal sites.<sup>21,22</sup>

### ABSENCE OF NATURAL IMMUNITY

Correlates of protection are generally modeled on natural restorative infection but for HIV there is no precedent for successful natural clearance. The best response that we can model for vaccination purposes are responses induced in subjects with HIV that naturally control virus to very low levels for long periods; so called long-term nonprogressors. However, several genetic factors appear to be important in this select group of individuals<sup>23</sup> and it is difficult to draw conclusive findings that will be directly relevant for vaccine control in the wider community.

Taken together, these obstacles are unprecedented and present a novel challenge to vaccinologists. Several of the obstacles are illustrated in Figure 16.1. An HIV vaccine that induces sterilizing



**Fig. 16.1:** Obstacles to HIV vaccine research. Several of the many viral and host factors that limit the generation of effective immunity to HIV are illustrated during the HIV life cycle of infecting a susceptible target cell.



immunity may not be possible in the short term. However, a partially effective vaccine that reduces viral load to below 1500 copies/mL of plasma will curtail sexual transmissibility of the virus and substantially slow progression towards disease in vaccine recipients.<sup>24,25</sup>

## Immune Correlates of Protective Immunity

A successful vaccine for HIV needs to safely and effectively establish durable and protective immunological memory to prevent infection and/or disease. The majority of successful vaccines have relied upon an empirical approach however as discussed above, the exceptional challenge of HIV vaccination has meant that such strategies have been unsuccessful. It is now widely recognized that new insights into protective immunity and a better understanding of the immune events that occur during HIV infection are required to drive advances in vaccine design.<sup>26</sup> Analyses of both human studies and NHP trials are dissecting immune correlates of protection and have obtained a better understanding of immune events during HIV infection. Several key differences in the immune responses of those who demonstrate some control over viral replication have been identified and will hopefully assist future HIV vaccine design.

### ANTIBODIES

NABs represent key immune correlates of sterilizing immunity for most traditional vaccines. Passive transfer of high titer broadly neutralizing NABs confers protection from SIV/SHIV in NHPs<sup>27</sup> and partially delays the recurrence of viremia in HIV-infected subjects taken off antiretroviral treatment.<sup>28</sup> Thus far, vaccination attempts have not led to the induction of broadly reactive NABs and hence their use at preventing infection is frustratingly limited. Broadly, cross-reactive NABs have been found to arise during chronic infection and periods of high plasma viral loads and, although generally present in low titers, may play a role in partially controlling viremia. However, the effects of NABs are generally limited due to the rapid ability of the *Env* protein to mutate.<sup>29</sup> Findings from the passive transfer of NABs have also indicated the importance of the Fc portion of the antibody<sup>30</sup> suggesting that not only is the neutralizing ability of the antibody important but also the effector function. Antibody effector functions mobilize other cells of the immune system to result in the phagocytosis of antibody-coated virions and the destruction of virally infected cells though antibody-dependent cellular cytotoxicity (ADCC). Indeed ADCC activity against SIV infection induced by vaccination of rhesus macaques has been shown to correlate to control of infection.<sup>31</sup>

### CYTOTOXIC T CELLS

Cytotoxic T lymphocytes (CTL) cannot completely prevent infection but do play a crucial role in controlling HIV replication. The emergence of this response corresponds with initial control of primary viremia as well as being critical in determining the

set point viral load that dictates subsequent disease progression. Depletion of these T cells leads to loss of viral control in SIV and rapid disease progression.<sup>32</sup> CTL escape mutants of HIV are continually selected and are temporally associated with loss of immune control of infection. Why some CTL responses are more effective at controlling virus replication than others is currently being explored. It is now clearer that the “quality” of the T cells (their capacity to accomplish many antiviral functions) is important in achieving control of viral replication. High quality CTL are highly cytolytic and capable of secreting numerous cytokines and chemokines (such as IFN $\gamma$ , TNF $\alpha$ , MIP-1 $\beta$ ) and display good proliferative ability.<sup>33,34</sup> There is also evidence that T cell receptor avidity and the differentiation status of the T cells is important. Indeed, inducing and maintaining “effector” CD8 T cells may decrease the incidence of SIV acquisition of monkeys.<sup>35</sup>

### CD4 T HELPER CELLS

CD4 T lymphocytes orchestrate immune responses and are hence regarded as “helper” cells. HIV-specific CD4 T helper cells have been associated with transient control of viremia during early primary infection after interruption of antiretroviral treatment.<sup>36</sup> However, CD4 T cells are also a target cell for HIV infection, and the subsequent loss of CD4 T cells impairs the CD8 cytolytic T cell response.<sup>37,38</sup> Mechanisms to retain HIV-specific CD4 T cells early in infection are likely to contribute to the control of disease progression.

### HOST FACTORS

Numerous genetic factors have been demonstrated to correlate with different disease outcomes in HIV infection. The HLA type of an individual can have a profound effect on the course of disease. For example, HLA-B57 and HLA-B27 are associated with HIV control whereas HLA-B35, 45, and 53 are associated with HIV susceptibility.<sup>23</sup> Favorable MHC molecules present conserved viral epitopes to CTLs. Killer cell immunoglobulin like receptors (KIR) are expressed on natural killer cells and one KIR (KIR3DS1, which interacts with a particular HLA allele) is associated with HIV exposed but uninfected subjects.<sup>39</sup> Ways to manipulate these genetic factors for improved vaccine design are currently being explored.

It is imperative to establish immune correlates to facilitate and interpret future clinical trials. However, immune correlates may only emerge in the context of successful vaccine efficacy studies in humans. Reliable and robust assays to measure immune responses must be in place to enable dissection of immune correlates. There may be interactions between apparently effective immune responses that make dissecting the precise correlates of protective immunity difficult. In particular, correlates of protection involved in preventing disease progression during natural infection with HIV may not reflect those that would be protective in the presence of pre-existing vaccine induced immunity. These are substantial research issues for the coming decade.

## Failed Efficacy Trials of HIV Vaccines

Three HIV vaccine strategies have reached human trials where the efficacy of the vaccine is evaluated in large numbers of HIV-uninfected subjects at high risk of infection. Two strategies have been reported and one is ongoing. Both reported strategies showed no reduction in rates of HIV infection, although many important lessons were learnt for future studies.

### GP120 PROTEIN TRIALS

The two VaxGen trials assessed a series of vaccinations with recombinant HIV-1 Envelope *gp120* proteins in an alum adjuvant. This was an approach to induce neutralizing antibodies, based in part upon the highly successful hepatitis B surface protein vaccines. The first trial was initiated in North America in 5403 people, primarily at risk of HIV through male-to-male sexual activity. An overlapping trial was initiated in Thailand, involving 2546 people, primarily at risk of HIV through injecting drug use.<sup>40</sup> These huge trials were conducted successfully,<sup>41</sup> paving the way for future large-scale trials of biomedical prevention strategies.

No efficacy in either study was demonstrated; for example, in the Thai study there were 106 new HIV infections in the vaccine group and 105 new infections in the placebo group (Table 16.1). The lack of efficacy was interpreted as insufficiently broad neutralizing antibodies induced by the protein vaccination.<sup>42,43</sup> Earlier studies *in vitro* and *in vivo* in chimps showed some induction

of neutralizing antibodies, but these responses were subsequently shown to be limited primarily to lab-adapted strains of HIV. When the antibodies were tested against “primary” isolates of HIV-1 (i.e., not cultured in the laboratory and expected to be encountered in real-world), no effect on inhibiting HIV infection was apparent. This lack of induction of neutralizing antibodies capable of broadly inhibiting primary HIV-1 isolates still haunts the field today.

### VIRAL VECTOR TRIALS

Disappointing results with inducing neutralizing antibodies have led to a rethinking of HIV vaccine strategies. Many studies are now focusing more carefully on T cell immunity to HIV, since T cell immunity is linked to control of virus replication. Recombinant viral vectors, where HIV genes are expressed from within other viruses, are frequently used to induce T cell immunity since the expression of foreign antigen within infected cells leads to more efficient presentation to CD8 T cells. Several types of attenuated poxvirus vectors have been used, with variable success in inducing T cell immunity. One of these, an avian poxvirus termed canarypox, has proceeded into a human efficacy trial in Thailand.<sup>44</sup> This large phase III trial involves priming the immune response with a canarypox that expresses multiple HIV antigens and then boosting antibody responses with the *gp120* protein vaccines used in the VaxGen trials. 16,402 volunteers participated in the trial, which opened in 2003. Half of the volunteers received the vaccine (RV144:ALVAC+AIDSVAX) and half placebos; all were counseled on HIV prevention. Of the 8198 people injected with the placebo, 74 contracted HIV; of the 8197 who got the vaccine, 51 got the virus—a 31.2% reduction in infection ( $p = 0.04$  in primary analysis).<sup>45</sup> Further studies are now planned to tease out potential immune correlates of the protection observed and expand upon these findings.

A second generation of viral vector vaccines used replication incompetent adenovirus vectors. Phase I/II human trials showed these vectors were more efficient at inducing T cell immunity compared to most previous poxvirus vaccine trials. The first efficacy trial of this approach (the “STEP” trial, conducted primarily in North America) was terminated in late 2007 when no efficacy was observed.<sup>46</sup> A second efficacy trial of the same approach (the “Phambili” trial in South Africa) was in the process of enrolling subjects when results of the STEP trial were announced and this trial was also discontinued. Subgroup analyses of the STEP trial showed modestly increased rates of infection in vaccine recipients with prior adenovirus immunity or who were not circumcised. Being uncircumcised is a clear risk factor for HIV acquisition.<sup>47</sup> Earlier monkey-SIV studies had showed some efficacy of this adenovirus vaccine approach, particularly for reducing virus levels after infection.<sup>48</sup> However, efficacy was improved with this approach if prior priming of the immune system with a DNA-based vaccine was used (a so-called “prime-boost” T cell immunity approach shown to be highly immunogenic in monkeys<sup>49</sup>). A smaller efficacy trial has now started based on a multicomponent DNA

**Table 16.1:** Human Efficacy Trials on HIV Vaccines

Efficacy trial (reference)	Vaccine	Number of subjects	HIV infection rate vaccine	HIV infection rate placebo
VaxGen - North America {Flynn, 2005 #6380}	<i>gp120</i> proteins: 2 B clade proteins	5403	6.7%	7.0%
VaxGen - Thailand {Pitisuttithum, 2006 #6008}	<i>gp120</i> proteins: B clade and A/E clade	2546	8.4%	8.3%
Merck - STEP trial (HVTN 502) {Buchbinder, 2008 #6247}	Adenovirus type 5 vector expressing Gag, Pol, Nef	3000	3.2%*	2.8%*
Canarypox prime/ <i>gp120</i> boost	Canarypox vector expressing HIV antigens followed by <i>gp120</i> protein boost	~16,000	0.19%	0.28%
VRC/ HVTN505	DNA prime/ adenovirus type 5 boost	~1350	Trial ongoing	Trial ongoing

\* Primary endpoint rates were in those without prior adenovirus immunity.

prime/adenovirus boost vaccine.<sup>50,51</sup> Given the uncertainty surrounding the predictions of efficacy of HIV vaccines and the costs associated with such massive field trials, there is now a move towards smaller efficacy trials to show some benefit (so-called “test of concept”, or phase IIb trials) before larger, licensing trials (phase III trials) are undertaken.

## Vaccine Strategies in Preclinical/Early Phase Clinical Trials

### TRADITIONAL APPROACHES

Simple protein and whole inactivated virus vaccines are not protective in macaques. Live attenuated SIV viruses containing deletions in the Nef protein are, however, highly protective in macaques against a high-dose intravenous challenge with pathogenic SIV,<sup>52</sup> and to a lesser extent against heterologous SIV challenge viruses. However, such live SIV attenuated vaccines can eventually cause AIDS in a proportion of infant and adult macaques.<sup>53</sup> Further, humans with naturally acquired Nef-deleted variants can also eventually progress to AIDS.<sup>54</sup> More highly attenuated strains are unfortunately less protective in macaques. Efforts to produce “conditionally replicative” attenuated HIV strains are ongoing,<sup>55</sup> although it is unlikely that a live attenuated vaccine for HIV will proceed to human trials in the foreseeable future.

### INCREMENTALLY IMPROVED VACCINE STRATEGIES

A variety of newer approaches are being attempted to improve the efficacy of traditional approaches. Over 18 human HIV vaccine trials involving over 2500 participants have been completed since 2003 (see [www.iavi.org](http://www.iavi.org) and [www.hvti.org](http://www.hvti.org) for recent and current approaches). Currently, the HIV Vaccine Trials Network lists ongoing HIV human vaccine trials involving approximately 4500 participants. Many current approaches involve adenovirus based and/or DNA plasmid vaccines expressing a range of HIV proteins primarily aimed at stimulating T cell immunity.

Common themes amongst recent and ongoing trials, shown in Table 16.2, include (i) DNA delivery of antigens, (ii) DNA vaccine prime followed by a boost with various recombinant viral, plant, and bacterial vectors, (iii) augmentation of immune responses using novel adjuvants and/or cytokines, and (iv) the development of improved delivery systems to enhance immunogenicity (e.g., vaccines guns, virus-like-particles). DNA vaccines have generally been weakly immunogenic in humans, although electroporation of the DNA into the skin and the use of cytokines such as IL-15 have substantially improved their immunogenicity.<sup>56,57</sup> DNA prime/poxvirus boost regimens have been assessed in several phase I/II trials with mixed results. Phase II studies from an Oxford group using a DNA prime/attenuated vaccinia virus boost approach showed disappointing immunogenicity<sup>58</sup> although related trials are ongoing.<sup>35,56,59–73</sup>

**Table 16.2:** Selection of Newer HIV Vaccine Concepts<sup>35,56,59–73</sup>

Effector mechanism	Concept	Comment (reference*)
T-cell	<u>Improved vectors/antigens</u>	
	Modified vaccinia vectors	Modified to reduce expression of irrelevant antigens <sup>60</sup>
	Simian CMV	CD8-independent effector memory T-cells <sup>35</sup>
	<u>Multiple epitope vaccines</u>	
	Universal T-cell vaccine	DNA “Polytope” of over 200 CD8 epitopes <sup>61</sup>
	Polytope “coldspot” vaccine	Targets recombination “coldspots” within HIV <sup>62</sup>
	<u>Mucosal administration routes</u>	
	Nasal/vaginal/aerosol delivery	Increased mucosal response <sup>63–65</sup>
	<u>Augmentation of responses</u>	
	Electroporative delivery	Enhanced delivery of DNA to cells <sup>66</sup>
	Cytokine co-expression (e.g., IL-15)	Boosting T cell immunity <sup>56</sup>
	Nanoparticles	Protects antigen delivery to dendritic cells <sup>67</sup>
	<u>Novel host target</u>	
Neutralizing antibody	LINE-specific T-cells	Targets HIV-induced cellular proteins rather HIV itself <sup>68</sup>
	Reverse immunization	DNA construct to express mAb <sup>59</sup>
	Immune complexes	Antibodies complexed to gp120 with adjuvant <sup>69</sup>
	Self replicating alphavirus/HIV chimera	Replication stops when immunity neutralizes vaccine <sup>70</sup>
NK cell	Anti-lipid antibodies	Target cardiolipin on host monocytes to block infection <sup>71</sup>
	NK killing mediated by ADCC	Utilizes NK cells from innate immunity <sup>72</sup>

\*Adapted from a review of the HIV Vaccine Conference in 2008.<sup>73</sup>



## INNOVATIVE VACCINE STRATEGIES

There is a sense among HIV vaccine researchers that lateral thinking towards untried vaccine concepts may be required to induce effective immunity.<sup>26</sup> Scientific endeavor is in part shifting towards novel forms of vaccination that induce different types of immune responses. Some of the novel (and largely untried) concepts currently being evaluated are also summarized in Table 16.2 and include: (i) non-protein targets such as cardiolipin and other lipids, (ii) utilizing other arms of the immune system such as antigen presenting cells, NK cells and neutrophils, (iii) reverse immunization by the expression of antibodies from within persistent vectors,<sup>59</sup> (iv) targeting immunity against host cellular proteins required for HIV replication, (v) using gene therapies to enhance host immunity, (vi) using vectors with prolonged expression that stimulate durable immunity,<sup>35</sup> and (vii) self-replicating viral vectors that partially mimic the genetic diversity seen in natural infection. Many of these concepts have serious logistic and safety concerns, but hopefully they will identify key elements of protective immunity so that safer and simpler vaccines can then be designed.

## Logistic Issues Surrounding Availability of HIV Vaccines

If and when an HIV vaccine becomes available, delivering such a vaccine to those most at risk poses significant additional hurdles. First, the vaccine must be safe and acceptable to regulatory authorities. Many current HIV vaccines involve vectors or formulations that are untested in large numbers of people. There may be additional safety requirements for such novel vaccine designs. Second, the scale-up of manufacture required to deliver large numbers of doses globally is a significant hurdle. Many new vaccine types have not undergone successful scale-up of manufacture and new plants and processes may need to be developed, which could be both time-consuming and expensive. Third, delivering a vaccine to at-risk groups will be very challenging. Vaccine research and development is expensive and usually conducted by for-profit pharmaceutical agencies. As such, the resulting new vaccine is typically expensive, at several hundred US dollars per dose, and therefore unaffordable by many countries for widespread use. A pricing and payment structure will need to be put in place or vaccine delivery will be further slowed. Fourth, early generation HIV vaccines may not be fully effective, and how a partially effective HIV vaccine will impact on the epidemic is unclear. One problem with partially effective vaccines is that, once available, proving that another vaccine is more effective usually requires massively large clinical trials. Further, if the effect of the vaccine is short-lived, repeated vaccinations may be necessary to sustain reduced rates of transmission. This may be a particular problem with many vector-based vaccines since development of immunity to the vector limits the utility of revaccination.

## Conclusions

This chapter outlines many challenges surrounding the development of a safe and effective HIV vaccine. No HIV vaccine exists and recent failures of efficacy trials do not inspire great hope that an HIV vaccine will be available (and deployed) in the foreseeable future. Nonetheless, the intense global research effort, the improved understanding of factors that can partially control HIV infection, and the pipeline of highly novel vaccine approaches suggest that there is room for cautious hope that a vaccine will eventually be forthcoming.

### Summary

- There is no vaccine yet for HIV.
- There are many obstacles to developing a safe and effective HIV vaccine.
- The type of immunity required to control HIV is unclear, although both antibodies and T cell immunity can assist control of HIV.
- Three completed efficacy trials of HIV vaccine in humans failed to demonstrate protection; one completed trial showed modest efficacy and one trial is ongoing.
- Many HIV vaccine approaches are being tested in preclinical models and small human trials, with a renewed focus on developing innovative approaches.

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# 17

## Partner Notification for Sexually Transmitted Diseases

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### Introduction

Partner notification for sexually transmitted infections and diseases (for convenience, we will abbreviate as STDs) is not a controversial concept with respect to infection control or patient care. Infected patients, their sex partners (infected or not), healthcare providers, and public health agents typically agree that partners of infected persons should be informed of their exposure and referred for evaluation and treatment.<sup>1–4</sup> Moreover, the mechanics of notification are theoretically uncomplicated. In the United States, for example, a palm-sized referral card can contain comprehensive instructions for an appropriate remedy tailored to local conditions in just about any jurisdiction in the country. Finally, in considering phases of an epidemic,<sup>5</sup> partner notification is an intervention suitable for all phases.

Data, however, are hardly consonant with the smooth progress of partner notification. Although many patients and partners hypothetically agree with in-person notification, studies with estimates of the proportion of partners who get either notified or treated suggest fewer than half of sex partners are notified of infection and seek evaluation.<sup>6–9</sup> These studies are typically of patient referral for gonorrhea or chlamydial infection. Public health staff are generally insufficient to cover the range of infections: in the United States; most people with primary or secondary syphilis are interviewed, but a distinct minority of people with any other bacterial infection receive similar services.<sup>10</sup> From another perspective, too few clinic attendees identify themselves as persons notified by either a sex partner or a trained public health professional to believe that partner notification works as well as one would hope. Direct documentation is hard to find, but one paper found fewer than 20% of syphilis cases detected in a US setting were due to partner notification.<sup>11</sup>

These problems are well-known, and, fortunately, many people have responded with various innovations. Such innovations, some in the guise of formal interventions, others in the form of programmatic changes, form the last of three parts in this chapter. This discussion includes efficacy, but also the transition to effectiveness and issues of appropriate coverage and scale for population-level prevention impact.<sup>12,13</sup> As these efforts are more meaningful when described in

context, we describe the role of partner notification in patient care and infection control in the first part of this chapter. In the second part, we include some of the history of partner notification, and its present status in different parts of the world and for different STDs. Finally, we have incorporated the role of partner notification in HIV infection into this chapter: HIV has been historically a special case, at least in the United States, and we discuss this history and more current efforts to integrate partner notification services for HIV with those for other STDs.

### Part I: Overview

#### RATIONALE FOR PARTNER NOTIFICATION

Partner notification serves individual-level, dyad-level, and population-level functions in healthcare provision. These functions are visible in the classic equation for infectious diseases,  $R_0 = \beta \times c \times D$ <sup>14</sup>.  $\beta$  refers to the per encounter infectivity of a pathogen,  $c$  refers to the rate of encounters, and  $D$  refers to the duration of infection. For STD, this translates to the product of the per sex act risk of transmission, the rate of sex partner change, and the duration of the infectious period of a given STD. The product, indexed as  $R_0$ , the reproductive number, indicates at what rates a disease or infection will either spread, die out or remain stable.

By notifying partners and bringing them to care, infected patients (hereafter index patients, see Table 17.1) and those partners individually receive health benefits through reduced odds of being reinfected (patients) and reduced odds of remaining infected (partners). In terms of the basic equation, the partner has  $\beta$  or  $D$  reduced in his or her personal equation, and  $D$  is also reduced at the dyad-level. At the population level, the reduction of  $D$  through treatment of infected partners reduces  $R_0$ , at least slowing the rate of infection. We can therefore say that partner notification confers benefits at the patient, partner, and community or population level. Ancillary partner services such as behavioral counseling affect other parameters in the equation. For example, if patients and partners begin to use condoms until in a closed, uninfected dyad (or larger sexual network, for that

**Table 17.1:** Nomenclature: Infected Persons and the Agents and Objects of Partner Notification (PN)

Infected persons	Agents of notification	PN type	Partners of infected persons
<b>Index patient</b> Index case Original patient	Public health staff, known as: <b>Disease Intervention Specialists (DIS)</b> , Communicable Disease Investigators (CDI), Public Health Investigators (PHI)	<b>Provider referral</b>	<b>Partners</b> (sex or drug-using), contacts
	Index patients	<b>Patient referral</b> , self referral	
	Physicians, nurses, public health nurses (excluding those trained as DIS), other mid-level providers	<b>Third-party referral</b>	

Note: Boldface terms are used as default terminology in this chapter.

matter), they will reduce per act infectivity. This reduction in  $\beta$  should be demonstrable at the population level if the intervention is sufficiently potent and widely applied.

We do not mean to imply that solutions are easily reducible to, say, better coverage in partner notification services. For example, in the United States, the current flat rates of gonorrhea across the last few years suggest that  $R_0$  is close to 1.0. That and the relatively low population prevalence ( $< 1.0\%$ ) raise the prospect that minor improvements in interventions such as partner notification and other partner services might tip the balance toward lowered incidence and prevalence. However, the pronounced racial and other disparities in American gonorrhea rates in the face of existing interventions<sup>15</sup> (e.g., partner notification) point toward the need for different interventions and combinations of interventions.

### TYPOLOGY OF PARTNER NOTIFICATION

If the point of notification is to bring sex or needle-sharing partners who need care into a system that provides it, the medium

through which one accomplishes notification varies. At one level, we can consider the role of the person who becomes the medium of notification: a public health staff person, the index patient whose partners are to be notified, or perhaps even the healthcare provider (Table 17.1). The suitability of each of these actors for conducting partner notification is largely driven by the healthcare and social structures in which they operate. Some proportion of the research and evaluation literature covered below addresses the efficacy of trained public health staff as agents who interview patients. They interview index patients for identifying and locating information about partners and notify those partners, while protecting the confidentiality of the index patient (Table 17.2). Beyond notification and referral, this approach can be used to uncover detailed information about networks, for example, a cluster of men with drug-resistant strains of HIV in Washington state.<sup>16</sup> In the United States, these staff are most commonly known as Disease Intervention Specialists (DIS), and the most widespread description of their notification activities is called provider referral (other terms include DIS-

**Table 17.2:** Principal Partner Notification Activities, Measures, and Outcomes

Phase	Activities			Common measures	Population Effects ( $\beta$ cD terms)
	Provider referral	Patient referral	Hybrids		
Identifying partners (sex or drug using)	Interview index patient	Patient receives instructions to notify partners	Interview index patient	1. Total Number of partners 2. Number of partners per index patient = <b>Contact Index</b>	N/A
Notifying partners	Public health staff locate and notify partners	Patient locates and notifies partners	Patient notifies partners; provider follows up with patient to ensure notification or contacts partners not notified by patient	1. Proportion of partners notified 2. Number of partners notified per index patient = <b>Notification Index</b>	Potential behavioral change may reduce rate of exposure (c)
Treating partners	Curative treatment for some STDs; entry to care for HIV			1. Proportion of partners infected and treated Number of partners infected and treated per index patient = <b>Brought to Treatment Index</b>	Cure reduces duration of infection ( <b>D</b> ); other treatment may reduce infectivity ( $\beta$ )
Collateral intervention	Education, behavior modification interventions, or social service referrals; spontaneous behavior modification by patient/partners			Varies	Improved healthcare-seeking reduces duration of infection ( <b>D</b> ); behavior change may reduce rate of exposure (c)



assisted referral and health department referral). This term should not be mistaken for activities conducted by healthcare providers, which we will call third-party referral. If the patient is the medium of notification, which is common for many infections, the most typical term is patient referral (self referral is also widely used). For this chapter, we will use provider referral, patient referral, and third-party referral.

The situation is made more complicated by differences in structural approaches to partner notification. In the United States, a reference to patient referral typically means leaving the patient to get on with the job, with either a brief instruction or suggestion from a healthcare provider and possibly an information card to give to that partner. Anecdotally, organizations like community clinics sometimes refer to this process as partner notification; the same term a categorical STD clinic would only use for provider referral. In the United Kingdom, the patient often remains the medium of notification, but the surrounding structure is different: an interview with a health advisor and later follow-up by that advisor with the original patient, during which the patient will be asked about referral actions. In many cases, whether the referred partner has sought care can be checked through clinic records and matched to the index case. Program managers in each country are thus describing quite different scenarios when they speak of patient referral as an approach to STD control. We cover these issues in more detail in Part II.

## PARTNER NOTIFICATION ACROSS STDs AND POPULATIONS

### Infections and Diseases

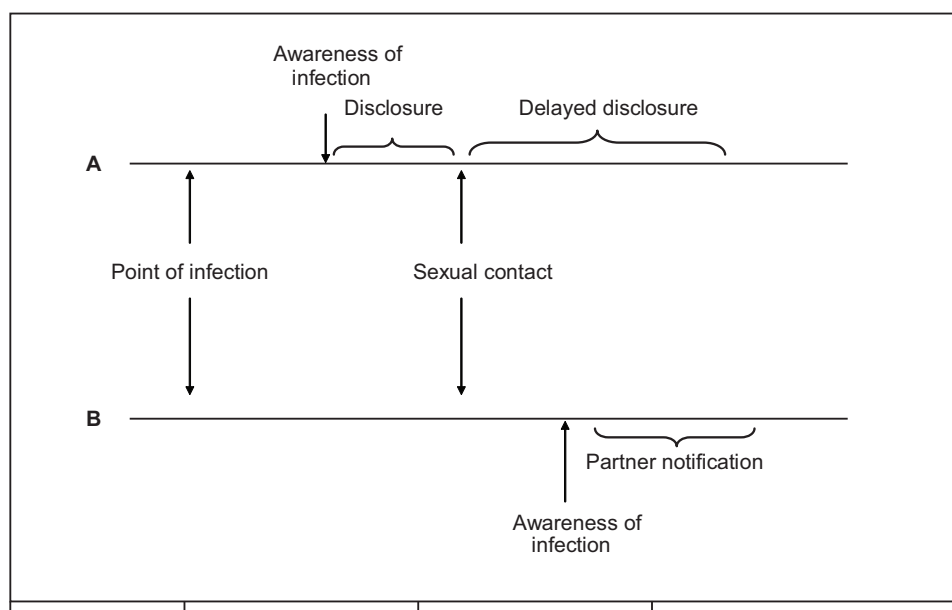
Many of the principles in provider, patient, and hybrid versions of partner notification apply across a range of STDs, including HIV. Nevertheless, differences among the effects of pathogens and differences among populations and sub-populations can change the odds of a given approach working or drive different approaches entirely. For example, the increase in the use of the internet for sexual partnerships in some countries may reduce the effectiveness of in-person provider referral, especially if the index patient has only an e-mail or screen name as identifying information. These conditions have also driven internet-mediated partner notification as a novel approach, both through DIS and patients.<sup>17,18</sup> Internet partner notification (IPN) is covered in more detail in Part III.

In the US and most other countries partner notification for chlamydial infection receives a lower priority than syphilis, HIV, or gonorrhea. Australian physicians routinely discuss partner notification for chlamydia-infected patients, but less than half provide referral cards, and most would find more resources useful.<sup>19</sup> In a 2001 survey of US health departments, composite statistics revealed 89% of syphilis patients, 52% of HIV patients, but only 17% of gonorrhea patients and 12% of chlamydia patients received any public health intervention such as an interview, a precursor to provider referral.<sup>10</sup> We have usually used these statistics to illustrate how the burden of STDs precludes

provider referral for all, but they also serve as a rough national prioritization. Compared to other countries, the US may be especially attuned to syphilis control, given the higher prevalence and particular historical circumstances. Nevertheless, whether syphilis serves as a reminder of past and continuing inequities<sup>20,21</sup> or as a sentinel event in countries with very low rates, syphilis cases tend to receive more attention than most other STDs, curable or not.

In 2007, the Community Guide to Preventive Services recommended provider referral as a strategy for finding previously undiagnosed cases of HIV.<sup>22</sup> The accompanying review estimated that about 20% of persons tested through provider referral were previously undiagnosed HIV-positive cases, making the strategy a relatively efficient means of bringing people to care.<sup>23</sup> In countries with access to care, the role of partner notification is therefore an important component of infection control and can be integrated with behavioral interventions.<sup>24</sup> Moreover, as HIV-infected individuals as a group tend to reduce transmission risk behaviors once they know their status,<sup>25</sup> notification has substantial collateral benefits for infection control. Current recommendations in the US suggest public health involvement with HIV partner notification, including early initiation of the process for individuals, once diagnosed, and use of surveillance data to generate cases for partner services programs. These points certainly do not preclude patient referral for HIV, as many patients will notify partners. Data included in the Community Guide review did point to a similar number of new positives per person tested via patient referral as for provider referral (there was an insufficient *quantity* of data to recommend the strategy). In the US, cost-effectiveness varies substantially, according to the prevention effectiveness as well as the level of fixed costs (e.g., DIS salaries). Figures generated in a recent review together with previous estimates, however, place almost all estimates at under US \$8000 per case detected (2007 dollars, with one outlier at \$22,000).<sup>26</sup> In developed economies, such figures are reasonable, considering value of entry to care and the prevention value of identifying people with HIV.

Discussions of partner notification sometimes include issues around disclosure, especially in the case of HIV (and some other viral infections). The most salient difference between partner notification and disclosure is the relationship between when a person becomes infected and when he or she actually knows he or she is infected. In Figure 17.1, Line A represents a continuum in which a person is infected and then aware of his or her infection *before* having sex with someone. Aware of his or her status, that person can now disclose infection status to the prospective: this is disclosure. Some researchers have observed that HIV status disclosure sometimes occurs after first sex with a new partner, but during the course of a relationship: this is delayed disclosure.<sup>27</sup> Line B in Figure 17.1 represents a continuum in which a person is infected and becomes aware of his or her infection after having sex with a partner. When that person uses some method of partner notification to make sure that partner is notified of exposure, he or she is using partner notification.



**Fig. 17.1:** Partner notification versus disclosure. Line A represents a continuum in which a person is infected and then aware of his or her infection prior to a new sexual contact. That person is in a position to disclose infection status to the contact, on a pre-contact (disclosure) or post-contact (delayed disclosure) basis. Line B represents a continuum in which a person is infected and becomes aware of his or her infection after a new sexual contact. Ensuring that contact is aware of his or her exposure constitutes partner notification. For curable infections and diseases, these distinctions become irrelevant for contacts that occur post-cure.

From the point of view of the partner, delayed disclosure and partner notification have some overlap. In both circumstances, people may switch between partner notification and disclosure situations for curable infections. That is, people perform partner notification for their sex partners prior to becoming aware of infection and disclosure for subsequent partners up to the point of cure. Thereafter, there is nothing to disclose. For those who become infected with HIV, however, there is no point of cure, and infected persons inexorably move into situations where disclosure is the relevant topic. This chapter is not the place to discuss Disclosure Research and other literature, but we note (a) HIV positivity disclosure is not a trivial undertaking for many people and (b) public health staff involved in HIV partner notification are dealing with people facing precisely that undertaking for the rest of their lives. The goals are the same, and much about HIV partner notification processes can be readily integrated with partner notification for other STDs (e.g., syphilis, gonorrhea, and chlamydial infection in the United States' 2008 recommendations),<sup>28</sup> but this is one important contextual difference that needs to be borne in mind for effective partner services.

Other viral infections are subject to the same parameters as HIV with respect to partner notification as a route to care rather than cure and in the matter of long-term behavioral change. Hepatitis C (HCV) partner notification efforts occur from time to time, typically in the context of a dense sexual or drug-using network, rather than as standard program practice. Likely, because investigation is rare and therefore undiscovered

infection is relatively prevalent, efforts can be rich in case-finding. A Dutch investigation of a man with acute HCV infection and rectal lymphogranuloma venereum (LGV) led to 16 other men, 7 of whom had been recently infected with HCV; 6 of these men had LGV proctitis and were seropositive for HIV.<sup>29</sup>

For herpes simplex virus (HSV) and human papillomavirus (HPV), partner notification, if it happens, will be almost exclusively via patient referral. For the patient, the balance of costs and benefits between notifying and not notifying partners differs by infection. HSV is responsible for morbidity *per se*, transmissible with or without symptoms, as well as being a known risk factor for HIV transmission.<sup>30,31</sup> Most authorities consider partner notification and disclosure generally helpful as a matter for patients and their partners, with physicians certainly advocating patient referral when they diagnose a patient.<sup>32</sup> Of course, this advice depends on a diagnosis, and many HSV cases remain either undiagnosed or not diagnosed until the patient has been infected for some time. In a recent Peruvian randomized, controlled trial (RCT), 25% of the sample were seropositive for HSV-2, but only 7% reported any ulcer symptoms (some of which were syphilis).<sup>33</sup> The value of partner notification as a means of population-level infection control is debatable without good data on what proportions of patients are diagnosed early after infection (i.e., before they have most likely transmitted the infection further). Information in this area is minimal.<sup>34</sup>

In contrast to the cases for HSV and HIV infections, HPV infection demonstrates a circumstance under which partner notification is *not* necessarily required. The rise in profile of HPV

stimulated a survey conducted for CDC in which physicians and mid-level providers (nurse practitioners, physician's assistants) were asked about various clinical preventive services and ancillary practices concerning HPV diagnosis.<sup>35</sup> Among the services were questions on partner notification practices of providers with their female patients diagnosed with HPV. In spite of the fact that partner notification for HPV has minimal theoretical impact (let alone empirically demonstrated impact) on population-level infection control and is of dubious value to male sex partners, analyses showed that over half of providers gave almost the identical patient referral instructions along the patient referral lines discussed above.<sup>36</sup> There is certainly no overarching reason why women should keep their infection status secret. Condom use may speed remission,<sup>37</sup> and, if (re)introduced into a long-term relationship, there will presumably be a discussion of why. The principal variables in the balance pertain to the woman's level of comfort discussing her infection, trust in her partner, and similar, patient-centered factors more relevant to disclosure than partner notification. Only if the relationship has ended or is likely to end is there a clear, partner-centered case for disclosing infection status.

## Populations

Priority populations vary according to local epidemiology and even societal norms and prejudices. In the US, CDC guidance on partner services does not set specific priorities, although people with repeat infections, acute cases of HIV (with potential for post-exposure prophylaxis with recent partners), or coinfections are typically prioritized highly in programs. Pregnant women or men whose sex partners are pregnant are also high priorities almost everywhere. The principal reason for the latter is, of course, the opportunity to reduce the rate of adverse outcomes of pregnancy attributable to STDs, but pregnancy is also a marker for unprotected sex. A New Zealand study of women presenting for abortion services found a 10% rate of STDs (8% chlamydial infection), demonstrating that women seeking these reproductive health services are also good candidates for testing and partner notification interventions.<sup>38</sup>

Domestic violence attributable to partner notification is assessed routinely by DIS, but less obviously so by providers giving advice to patients. Moreover, if index patients are the medium of notification, there is also the question of whether they will perpetrate violence. Complicating matters further is the endemic level of overt domestic violence in relationships. For example, one Kenyan cohort study looked at domestic violence as a predictor of vertical transmission intervention uptake among HIV-infected pregnant women.<sup>39</sup> Of 2836 women responding, 28% reported previous domestic violence. Although this was not statistically associated with decreased rates of partner notification (via patient referral), OR = 0.7, 95% CI = 0.5–1.1, women who were HIV seropositive were almost 5 times as likely to experience violence as those who were HIV seronegative, OR = 4.8, 95% CI = 1.4–16.0). Only 1% of women, however, actually reported violence

attributable to test results, and a South African study proactively assessing violence reported no adverse events from 106 women (10% of partners were “angry, embarrassed, or confused”).<sup>40</sup> A US study of Mexican American and African American women reported a high rate of physical or sexual abuse (63% lifetime), but this rate was not associated with partner notification.<sup>4</sup>

Although much partner notification research, especially its expansion into common STIs such as chlamydial infection, has centered around sex partners, one should not overlook its use in reaching needle-sharing partners in drug-related networks of infection. Such networks are sometimes characterized anecdotally as difficult and dangerous. But at least some evidence suggests that drug users are at least as cooperative as those with only sex partners. A Utah evaluation of HIV partner notification in which the two populations were explicitly compared found that 93% of drug users cooperated to the extent of naming partners, versus 76% of others (RR = 1.2, 95% CI = 1.1–1.3).<sup>42</sup> One might suspect these results were biased by confounds such as differential rates of gay men in the two groups. These data were collected between 1988 and 1990, at a point when the stigma attached to male homosexuality and HIV infection was still extremely high.<sup>43</sup> However, when controlling for this and other factors (e.g., age), the difference was still statistically significant. Utah HIV partner notification at the time was also a hybrid program in which index cases were interviewed, but chose patient referral versus provider referral. Across these notification methods, 74% of named partners were notified, with slightly higher rates among sex partners (75%) than needle-sharing partners (65%). Overall, the number of partners found per index case was highest among drug users (3.3), due to the larger number of partners named by drug users.

Finally, there is the question of partner notification for incarcerated persons, for migrants and for the homeless. In the US, people are sometimes screened for common STDs or HIV when being processed in the criminal justice system, and STDs such as syphilis are often concentrated in American jails.<sup>11,44</sup> Processing may simply be a matter of 24 hours in custody; if this is the case and test results are swift, the arraigned individual may receive patient referral instructions (whether he or she is in the mood to adhere to referral instructions is another matter). If test results lag by a period longer than the individual is in custody, then the infected patient may be informed of his or her status when contacted for, say, a court appearance, but the delay reduces the effectiveness of partner notification in infection control. Provider referral is possible and a more plausible means of notification if the individual is incarcerated for longer periods of time. One cost-effectiveness study in Massachusetts, US found that adding partner notification for female sex partners of male inmates resulted in no net costs (at the healthcare system level) when the benefits of detecting infection in partners was considered.<sup>45</sup>

Migrants and homeless populations are severely understudied with respect to implications for partner services. A 2007 study of HIV diagnoses in California found that immigrants (in this study, Hispanic) had delayed HIV diagnosis rates compared to

others, pointing to the need for integrated partner notification services across jurisdictions.<sup>46</sup> Interestingly, other than symptoms, the one factor in seeking testing was an STD/HIV diagnosis in a partner. The good news is that patient referral occurs among this population and drives testing. The bad news is that the evidence does not support the notion that the current rates of patient referral are enough. For those who migrate more frequently, complications include the potential for acquisition in one place, transmission in another, and diagnosis (if any) in a third place. Migrants, particularly if vulnerable to arrest and deportation, are at-risk for acquisition as well as a potential vector for transmission between populations (i.e., bridging).<sup>47</sup>

Many of these conditions around testing, treatment, and partner notification apply to the homeless as well. Some studies of contact tracing for tuberculosis among the homeless exist,<sup>48–50</sup> but STDs partner notification in this group is even less well-studied than migrants or the incarcerated. One Canadian study estimated homeless people in a shelter had an average of 97 contacts in any one day, rising to 120 over the course of a week.<sup>51</sup> The difficulties in tracking the index patients (let alone partners) after a week were substantial, as people tended to leave the shelter by 7 days. Although this paper was predicated on containing an airborne infectious disease (e.g., SARS, tuberculosis), the principle of patient transience and transient relationships still holds.

### Partner Notification Coverage and Scale

Ideally, all persons exposed to an index case would receive the most effective forms of partner notification. Often, this means provider referral or at least direct public health involvement in the notification and referral process. Resource constraints, however, mean that this relatively labor-intensive approach is cost-prohibitive for many programs. One then has to consider coverage issues: how many index cases must receive services in order to reduce future incidence and therefore exercise population-level STD control?

New York state data from the 1990s provide an example of such an exercise. Gonorrhea rates in New York state dropped substantially during the 1990s, as they did elsewhere in the United States, but analysts demonstrated that the proportion of index cases interviewed in a given year predicted incidence in the next year.<sup>52</sup> Specifically, a 10% increase in the number of partners treated (itself a function of the proportion of index cases interviewed by DIS) was associated with a 6% decline in gonorrhea rates. Collateral analyses put the necessary level of coverage, defined as proportion of gonorrhea index cases interviewed, to affect population prevalence at about 40% (with about 52% of partners medically evaluated and 30% administered prophylactic treatment). With respect to scope, New York also tested the effects of concentrating efforts in core areas, defined simply as areas of high prevalence, finding that core area approaches resulted in reduced subsequent prevalence compared to efforts to interview cases evenly across geographic areas.<sup>53</sup> Given the propensity for gonorrhea to be clustered geographically,<sup>54</sup> a core area approach on the grounds of scarce resources would seem to have wide merit.

Demonstrating that one can achieve sufficient coverage with one method to affect population STDs rates does not mean that only that method should be applied. A program's scope can include a minimum level of coverage of a method like provider referral and also include alternative methods for those not covered by provider referral. For example, New York's interview algorithms in public STDs clinics could cohabit with patient referral instructions, including referral cards and expedited partner therapy (EPT), with neither approach suffering because the other exists.<sup>55</sup> In the United States, the most recent recommendations for partner services suggest a variety of approaches tailored to local conditions, with the underlying premise that STDs program scope should consist of having some partner services protocol for HIV and several other STDs.<sup>28</sup> Sweden has addressed both scope and coverage of partner services for chlamydial infection through making physicians responsible for partner notification. That is, the coverage benchmark effectively became 100% of diagnosed cases, and scope of services included several provider and patient-mediated approaches, including patient referral instructions, physician-based notification and referral, and patient-delivered partner therapy (PDPT).<sup>56</sup> Ramstedt's evaluation of these approaches showed that each enhancement over no effort was associated with reduced reinfection rates (10% with no intervention, 8% with patient referral, 5% with physician referral, 2% with PDPT).

## Part II: History and Current Scope of Partner Notification

### PARTNER NOTIFICATION IN HISTORY

References to syphilis in Europe, including the knowledge that it was sexually transmitted, date back centuries,<sup>57</sup> and there remains something of a cottage industry in speculating about which monarchs, clerics, and other powerful figures were infected with syphilis before dying. Efforts to stem transmission, if any, were more attuned to isolating infected individuals during their symptomatic phases (if they were not too powerful to be thus bothered) and periodically pinning the blame for syphilis on prostitutes and other disfavored groups.<sup>58</sup>

No doubt some physicians asked their patients to tell their spouses of infection. In the absence of efficacious treatment, partner notification's role in stemming transmission relies on people eliminating or limiting the amount of sex they have, or at least avoiding new partners. Systematic efforts to have sex partners informed of their exposure date back to the early 20th century in Sweden, where partner notification became compulsory for syphilis and gonorrhea in 1918.<sup>59</sup> Both patients and physicians are legally responsible for notification; physicians can discharge their obligations by notifying a specified public health medical officer in writing.

In the United States, Thomas Parran, the Surgeon-General, took a different approach.<sup>60</sup> Parran conceived STD control as a public health concern, not as a moral imperative. By the end of



World War II, the US Public Health Service had trained a small cadre of (six!) professionals to interview syphilis patients about their sexual contacts and trace them—hence the term “contact tracing”—and refer them for treatment with penicillin.<sup>61</sup> This model with the DIS survives with relatively few modifications as a vital component of syphilis control today.

Most of the process and outcome indicators of partner notification activity identified in Iskrent and Kahn’s 1948 paper on the evaluation of syphilis control activities, such as the contact index, epidemiologic index and the brought to treatment index are still used as indices of provider referral success.<sup>62</sup> Other categories for the disposition of cases, for example, “out of jurisdiction,” are also those used currently. Only the lesion-to-lesion index (the number of primary or secondary cases found as a result of interviewing a primary or secondary case) is perhaps less widely used, although easily measurable. The lesion-to-lesion index is indicative of the speed as well as the success rate of provider referral for syphilis and, given the high value of detecting a case in primary or secondary stage (where most transmission takes place),<sup>11</sup> serves some role in measuring the effectiveness of a program in stemming transmission. Iskrent and Kahn cite an average of 0.14 (i.e., 14 primary and secondary cases found per 100 primary and secondary cases interviewed) around 1946; it is unlikely this rate would be exceeded today.

An advantage of method and measurement consistency is that comparisons across time have more meaning. Selecting here for a few investigations between the 1940s and the 1980s, we find investigations in Arkansas, US reporting a contact index of 3.26 for syphilis, with 324 infections found among 655 sex partners of 201 index patients.<sup>63</sup> Of those 324 infections, 167 (52%) were “brought to treatment,” the remainder were previously treated. A review of UK programs use the same data for the “Tyneside scheme;” here, the main infection is gonorrhea, there is some assessment of whether the contacts are same or opposite sex, and the contact index in 1970 is 1.35.<sup>64</sup> This review in particular covers 27 years of partner notification in northeast England and is one of the most comprehensive data-driven reviews in the field. The citation of 80% of contacts located and notified by public health staff in 1946 is close to US figures<sup>63</sup> and a reasonable benchmark for in-person provider referral for syphilis or gonorrhea today. Another 1972 review contains comparisons of STD rates across nations.<sup>65</sup> The resurgence of syphilis is noted, interestingly, the rates of resurgence ran higher in countries *without* established public health STD prevention (this is, of course an ecological comparison, and plausibly confounded with other social variables).

A 1977 RCT of patient referral with referral cards against provider referral suggested that the methods were equivalent.<sup>66</sup> The brought to treatment indices for previously undiagnosed infections in each RCT arm were almost identical, 0.25 for patient referral and 0.26 for provider referral, most seen within 2 weeks in both conditions. Results suggest clinic patients for whom follow-up is infeasible may not be harmed by patient referral,

but this was patient referral with some enhancements— referral cards and some time spent discussing the importance of partner notification. Later reviews suggest provider referral generally results in more cases seen.<sup>67</sup>

All the same, clinical situations often do not present a clear choice between provider referral and patient referral, nor is it clear there should be one. In Colorado, HIV patients in the 1980s discussed referral options with providers, arriving at a mutual decision.<sup>68</sup> Providers followed up on cases where patients had agreed to notify partners and vice versa. At one month, patients had notified 57% of the partners they had agreed to notify, and DIS had notified 85% of the partners they had attempted to contact. DIS following up with partners that patients did not notify brought the first total up to around 90%, and, interestingly, patients following up unsuccessful provider referral raised the second total also to around 90%. Although DIS clearly notified the majority of partners (80%), the larger point is that a program with early intervention (the interview), choice and a fallback option can do better than relying on a single strategy. For a similar perspective, a Swedish retrospective evaluation of various strategies showed how choice and informed discussion can strengthen partner notification for an infection as prevalent as chlamydia.<sup>56</sup> Swedish physicians could discharge their responsibilities in several ways at different time periods— third-party referral, contact slips, giving patients medications for partners, and each was associated with reduced index patient reinfection.

The Swedish experience with permitting patients to take medications to their partners during the 1980s is a reminder that what is thought of as innovation has often been tried before. On the publication of an RCT in 2005,<sup>69</sup> one of the authors (MH) received a letter from a physician in North Carolina. He referred us to a short paper he published in the *New England Journal of Medicine* in 1977.<sup>70</sup> The report referred to giving extra doses of medication for the “consorts” of women diagnosed with trichomoniasis. Among the 31 women who received extra doses, all who were tested were clear at an initial test of cure and 1 was subsequently found to be infected 10 months later. Two patients reported the partner refused to take medications, and those patients had no further sexual contact with either. The next piece of US research on the topic was published in 1998.<sup>71</sup>

## PARTNER NOTIFICATION TODAY: CURRENT SCOPE

The Community Guide for Preventive Services recommends provider referral for HIV,<sup>22</sup> and there are recent RCTs for innovative practices (see Part III). References for the effectiveness of provider referral for gonorrhea control often include a Colorado study in which the introduction of provider referral in a military setting resulted in a 20% decline in incidence among the civilians in the surrounding community.<sup>9</sup> There are, however, fewer reviews of the effectiveness of standard STD provider, other third party, and patient referral.

Brewer's 2005 review of case-finding effectiveness for syphilis, gonorrhea, chlamydia, and HIV identified brought-to-treatment indices of 0.22–0.25 for the first three STDs and 0.13 for HIV.<sup>72</sup> His review drew studies of program activities (mostly provider referral) between 1975 and 2004. This comprehensive review of program activities (mostly provider referral) serves as a baseline for our update. We searched the published literature between 2005 and February, 2009, searching for studies that described partner notification activities and linked them to outcomes. (The original version of this search produced evidence tables for the 2010 US STD Treatment Guidelines.)

We subsequently tabled 26 papers with partner notification interventions and outcomes. Many studies were easily categorized into the traditional provider-based (7 studies) and patient-based (11 studies) referral frames; these are in Tables 17.3 and 17.4 and form the database for estimating the current effectiveness of both forms of notification today. A further 8 studies are tabled separately to cover the UK audits of their partner notification system as a special evaluation of a national (i.e., population-level) control program.

### Provider Referral: Public Health Staff as the Medium of Notification and Referral

The 7 studies in Table 17.3 come from Sweden (2 studies) the US (5 studies) and include provider referral efforts for men and women, heterosexual men and MSM, diagnosed with syphilis, HIV, HBV, gonorrhea, or chlamydial infection.<sup>73–79</sup> Thirteen contact indices based on public health staff interviewing (median = 2.05) ranged from 0.5 for cases of acute HIV in San Francisco<sup>74</sup> to a substantial outlier, 6.8 for predominantly MSM diagnosed with syphilis across 8 US cities with reported outbreaks.<sup>77</sup> Seven of the 12 estimates fell between 1.0 and 3.0; there was no clear pattern by STD. Instead estimates tended to clump by study site; for example, the contact index of 0.80 for MSM diagnosed with syphilis in Georgia, US was closer to the 0.72 estimated for heterosexual syphilis-infected men in the same setting than almost any other estimate.<sup>75</sup> Although a contact index of <1.0 is often seen as an indicator of program failure, we shall see below (in *Program effectiveness*) that, if most contacts are notified and many are infected, provider referral based around low contact indices can indeed be useful.

**Table 17.3:** Provider Referral Partner Notification Studies Published Between 2005 and 2009

Citation/ quality	Study design	Population and setting	Exposure or intervention	Principal outcome measures	Principal findings	Miscellaneous design and analysis considerations
Sylvan & Hedlund 2009 <i>J Eur Acad Dermatol Venereol</i> <sup>73</sup>	Retrospective evaluation	Youth community based health offices Uppsala County Sweden. 463 cases CT (Female 299 and male 164)	Patient interviewed by sexual health advisor or physician	Number of: contacts, successfully contacted partners, and accuracy of the numbers reported for unsuccessful contacts	Contact index (female) = 2.21 (660/299). Contact index (male) = 2.36 (386/164). Successful partner notification 73%	Originally, 52% of female's partners and 20% of male's partners incorrectly recorded as unsuccessful partner notification
Ahrens et al. 2007 <i>JAIDS</i> <sup>74</sup>	Retrospective evaluation	763 HIV patients San Francisco 2004–2006	Patients interviewed for partners with HD follow-up offered	Patients interviewed, partners elicited and tested	79.6% (607/763) patients interviewed Contact index for acute cases = 0.5 (15/30); non-acute = 0.85 (339/398); long-standing = 1.65 (553/335) 13% of partners for acute and non-acute newly diagnosed with HIV NNTI = 25 (acute), 21 (non- acute), 39 (long-standing)	
Samoff et al. 2007 <i>Sex Transm Dis</i> <sup>75</sup>	Retrospective, record review	401 index male syphilis patients; MSM (243) or MSWO (158); Atlanta, GA	Health department staff interview patients for partners	Partners notified and tested	Contacts located for MSWO 90 (77%) and for MSM 159 (77%)	Almost identical case- finding, but a larger proportion of MSM partners not followed up
Gunn et al. 2006 <i>Sex Transm Dis</i> <sup>76</sup>	Prospective evaluation	190 reported cases of chronic HBV (aged 15–45) in high-morbidity communities, San Diego, CA 1999–2000	Patient interviewed for partners by public health staff, who follow- up with partners (partners within past 1 month)	Partners notified, beginning treatment, completing treatment	129/190 cases interviewed; 85 reported partners in past 1 month; 46 accepted PN services and named 47 partners; 38/47 partners were notified; 14/15 eligible began treatment (9 completed)	Treatment constituted a series of 3 vaccinations for HBV

(Continued)

Citation/ quality	Study design	Population and setting	Exposure or intervention	Principal outcome measures	Principal findings	Miscellaneous design and analysis considerations
Hogben et al. 2005 <i>Sex Transm Dis</i> <sup>77</sup>	Retrospective evaluation (aggregate of 8 cities)	1517 MSM patients with early syphilis, 8 US cities	Public health staff interview patients for partners and conduct follow-up	Partners notified, tested, cases found	Contact index = 6.8 (10,254/1517) Median notification index = 0.94 Median cases found per index case = 0.26 (includes previously treated), 0.09 (excludes previously treated)	Study is a review of PN in cities with syphilis outbreaks; contains evaluation data for 8 cities. Median proportion of all partners claimed who were notified = 14%
Brewer et al. 2005 <i>Sex Transm Dis</i> <sup>78</sup>	Randomized, controlled trial	123 STD clinic patients (syphilis, GC, CT) reporting multiple partners in past 3 months, Colorado Springs, CO 2000–2001	DIS interviews with mnemonic cues: 1. Individual characteristics 2. First names 3. Alphabetic, location, network, roles	Partners elicited, located and notified  Outcome data include the increment for each experimental condition and the final index for each condition	Incremental contact index per condition (final index): 1. 0.28 (2.73) 2. 0.29 (2.14) 3. 0.57 (2.80) Incremental notification index per condition (final index): 1. 0 (1.02) 2. 0.10 (1.12) 3. 0.12 (1.51) $P < 0.05$	56% (82/145) of partners across conditions were infected
Osterlund et al. 2005 <i>Int J STD AIDS</i> <sup>79</sup>	Prospective evaluation	676 persons diagnosed with CT (any setting) Varmland Co., Sweden 2001	Trained midwives conduct interviews and notify partners	Partners elicited, notified and treated	Contact index = 2.05 (1389/676) 73% (1017) of partners were tested; 62% of these were CT- positive and treated	Data are compared to 1999 data in which physicians conducted PN (contact index = 1.56, 67/43)

GC, gonorrhea; CT, Chlamydia; NNTI, number needed to interview (to find an infected case); MSWO, men who have sex with women; MSM, men who have sex with men.

**Table 17.4:** Patient Referral Partner Notification Studies Published Between 2005 and 2009

Citation/ Quality	Study design	Population and setting	Exposure or intervention	Outcome measures	Principal findings	Miscellaneous design and analysis considerations
Thurman et al. 2008 <i>Int J STD AIDS</i> <sup>81</sup>	Cross sectional analysis	166 pregnant females with STI San Antonio, TX	Interview within 1 month of diagnosis (treatment or retreatment provided as needed)	Reports of intent to notify partner, partner notification	136 had 1 partner; 30 with multiple partners. 88.2% with 1 partner notified partners versus 54.5% of those with multiple partners	3 variables predicts PN: steady relationship, 1 partner and recent activity
Harry & Sillis 2008 <i>Int J STD AIDS</i> <sup>82</sup>	Retrospective study	60 (17 female, 43 male) newly diagnosed HIV patients – Bure Clinic East Anglia (UK) 1997– 2004	Patients counseled, patients responsible for referring partners	Partners notified	Overall, 31/60 (51.7%) reported notifying partners. PN reported by 23/60 (38.5%) homosexuals 15/60 (25%) bisexuals and 34/60 (57.1%) of heterosexuals	Small cohort over a long period of time
Niccolai et al. 2008 <i>Prev Med</i> <sup>83</sup>	Survey	135 CT- positive women, Connecticut, USA 2005–2007	Prospects of patient referral: patient-reported intentions to notify partners	Proportion intending to notify (includes self-reported notification), correlates of intention	Patients reported 187 partners and intended to notify (or reported already notifying) 75% of them; Relationship length and perceived quality were associated with positive intentions in multivariate models	Other indicators of relationship nature and quality were associated with intentions in univariate analyses

Citation/ Quality	Study design	Population and setting	Exposure or intervention	Outcome measures	Principal findings	Miscellaneous design and analysis considerations
Bakken et al. 2008 <i>Scan J Infect Dis</i> <sup>84</sup>	Longitudinal case series study	81 CT positive men identified in another cross- sectional study; 2005	Participants interviewed on PN intentions at tx visit and on PN actions at the test-of-cure visit; questioned about sex partners during the last 6 months	Partners notified and treated	65 interviewed at tx visit reported they intended to notify 100/165 partners (61%); the 35 interviewed at test-of-cure visit reported 63/95 (68%) partners notified	Original study included 1032 sexually active men, 18–30 yr, recruited at university in Oslo and Trondheim, Norway; CT tests positive for 81 men; 10% of tests-of- cure were positive confirming need for repeated treatment; men with 3 or more partners more often reported they did not inform all partners compared to men with few partners
Menza et al. 2008 <i>Sex Transm Dis</i> <sup>85</sup>	Retrospective evaluation	313 MSM reported with GC or CT and reported partner information; Seattle and KingCounty in 2004	Reviewed records of all MSM with GC or CT infection interviewed; men asked to indicate if each sex partner was already notified or treated at time of interview and were offered PN assistance	Partners reported by index cases notified and treated; DIS disposition codes	1037 partners reported; information provided for 634/1037 ( 61%); 213/313 (68%) of index patients reported notifying at least 1 partner; index cases reported that 295/1037 (28%) reported partners had been notified and 170 (16%) were treated; DIS disposition codes documented 111(11%) partners tx; only 18 index requested DIS assistance – DIS notified and tx 24/35 (69%) partners reported by those 18	409 MSM with GC and CT; only 313 reported partner information; higher levels of partner tx reported by index cases than DIS disposition codes
Thurman et al. 2008 <i>Sex Transm Dis</i> <sup>41</sup>	Cross- sectional analysis	775 low- income Mexican American and African American women with non-viral STD; age 15–45	Comprehensive intake interview to identify demographics and partner information; statistical analysis to determine factors independently associated with PN	PN; Factors associated with PN; identify women most likely to notify their partners about STI exposure	1122 male sex partners; of the women with 1, 2, or 3 partners, 87.9%, 41.4%, and 25% reported PN for all partners respectively; 5 variables predicted PN committed relationship, 1 partner, recent intercourse, anticipated ongoing sexual activity, desire for pregnancy; patient and partner sociodemographic variables not significantly associated with PN	Among low-income MA and AA women, perception that a relationship was committed was most predictive of PN; only assessed woman's intention to notify and could did not confirm if partner notified and treated
Young 2007 <i>Int J STD AIDS</i> <sup>40</sup>	Prospective evaluation	626 women, age 14–25 years old  Gugulethu, Cape Town, South Africa	Women testing positive for GC, CT, or trichomonas given choice of patient-based partner referral (PBPR) or patient delivered partner medication (PDPM); surveyed about experiences with either type of PN at f/u visit	Effectiveness, acceptability, and feasibility of PBPR and PDPM	PN choices recorded for the 106 women w/ at least 1 STD; 116 reported partners; 99 (85%) chose PDPM; 15 (13%) chose PBPR; 98 (87 PDPM, 7 PBPR, 4 both) of 106 women interviewed at f/u; 94% of partners exposed to PDPM took meds; 92% exposed to PBPR attended clinic for tx	Article includes patients' and partners' attitudes about both forms of PN
Balkus et al. 2006 <i>Sex Transm Dis</i> <sup>86</sup>	Retrospective evaluation (prospective cohort)	333 HIV- positive women who had recently delivered children. Nairobi, Kenya. 1999–2003	Patient referral	Index patient report of partners notified	76% of women using hormonal contraception reported informing partners; 80% of women not using hormonal contraception reported the same	Parent study evaluated HIV vertical transmission intervention. Study results indicate some partners were tested for HIV, implying some partners were notified

(Continued)



Citation/ Quality	Study design	Population and setting	Exposure or intervention	Outcome measures	Principal findings	Miscellaneous design and analysis considerations
Rose et al. 2005 <i>NZ Med J</i> <sup>38</sup>	Retrospective evaluation (chart audit)	77 women attending clinics specializing in termination of pregnancy, New Zealand 2003	Health interview, but partner management strategy unclear	Partners treated	42% (32/77) of women had a partner treated (verified)	Study notes that information on partner management was hard to extract from patient records
Gotz et al. 2005 <i>Sex Transm Dis</i> <sup>29</sup>	Prospective evaluation	165 CT- positive case reports (122 female), Netherlands (national sample) 2002–2003	Patient referral with referral cards, patient and healthcare worker discuss PN and elicit number of partners	Partners treated	86/176 (49%) partners were verifiably treated	A further 28 partners were “potentially” treated, manner of supposition undefined
Penney et al. 2005 <i>Public Health</i> <sup>87</sup>	Random sample-based survey	263 clinicians Lothian/ Grampian, UK 2002	Reported extent to which physicians (or designated staff) discuss PN with CT-infected patients	PN instruction rate	138/263 (52%) physicians reported PN discussions with patients	Survey response rate = 72%
McCadden et al. 2005 <i>Sex Transm Dis</i> <sup>88</sup>	Prospective evaluation (based on national screening sample)	65 CT- positive persons, UK 1999–2001	Cases notified and referred to general practitioner (50) or GUM clinic (15). PN discussed with study nurse and with healthcare provider	Partners notified (combination of clinic/ provider reports and study-related reinterview with patient)	49/65 (79%) patients had notified partners	Treatment verified for a proportion of partners, based on patient report

Notification indices (9 estimates, median = 1.02) ranged from 0.57 for heterosexual men with syphilis in Georgia to 1.65 for people diagnosed with chlamydia in Varmland, Sweden. As a proportion of partners named, figures ranged from 14% in the 8-city study<sup>78</sup> to 81% with HBV partners in San Diego.<sup>76</sup> Five of the 9 figures were above 70%, indicating that DIS or other public health staff found most of the partners they attempted to find. Of the remainder, a Colorado RCT produced figures of 37%, 52%, and 54%,<sup>78</sup> showing the outbreak figures from the 8-city study as an outlier. The actual notification index for that study was 0.94, close to the median; the high contact index (6.8) as a denominator reduced the figure as a proportion of partners named.

Finally, 7 estimates of the brought-to-treatment index (BTI; median = 0.22) ranged from 0.03 for long-standing HIV in San Francisco<sup>75</sup> to 0.93 for chlamydia in Varmland, Sweden.<sup>79</sup> The median is almost identical to the summary figure reported in Brewer's 2005 review.<sup>72</sup> For 3 estimates, all for syphilis, the authors reported infected partners' status according to whether the locating DIS found an infected, untreated partner or one who had been infected, but already treated diagnosed elsewhere at the time of notification. In one study, the BTI (Table 17.2) dropped from 0.26 to 0.09 when previously diagnosed partners were excluded; in the other, 37% of infected partners of heterosexual men and

59% of infected partners of MSM had been diagnosed elsewhere at the time of notification.<sup>75,77</sup> What appears to be a mixture of provider referral and patient referral is a reminder that both forms of referral can complement one another. Each notification strategy in the above examples, however, was reliant on an interview with health staff. This point is borne out further in a Seattle study in which HIV-infected index patients who reported talking to health department staff about partner notification were more likely to notify at least one partner than those who did not (OR = 2.5, 95% CI = 1.6–3.9).<sup>80</sup>

### Patient Referral: The Index Patient as the Medium

In this section, we evaluate studies that simply rely on the patient to notify partners without interviews or the potential for DIS follow-up of partners the index patient does not notify. Beside contact indices when there was some record of partners named, we examined measures of how many patients notified partners and, reported partner treatment rates and, in some studies, the reinfection rate among index cases.

The 12 studies in Table 17.4 come from seven countries and include patient referral efforts for heterosexual men and women and MSM diagnosed with STD including gonorrhea, chlamydial

infection, and trichomoniasis.<sup>29,38,40,41,81–88</sup> Six contact indices based on partners claimed at the time of diagnosis (median = 1.45) ranged from 1.07 for Dutch men and women<sup>29</sup> to 3.31 for MSM diagnosed with gonorrhea or chlamydial infection in Seattle.<sup>85</sup> The proportions reporting notifying partners was quite high (10 estimates: median = 64%), ranging from a low of 25% for women in Texas, US with 3 or more partners to 88% for women reporting 1 partner in the same study.<sup>41</sup> Three of the 4 estimates falling below two-thirds were based on people with multiple partners.<sup>41,81,82</sup>

One lesson from these figures is that patient referral efficacy is reasonable for index patients with a single partner, but drops sharply for those with multiple partners. Another lesson is that choice, again, may play a role in efficacy. The highest treatment rates were reported from a South African study in which women chose either a referral card for each partner (15 women chose a card for at least 1 partner) or medications to bring to a partner (99 chose this option for at least 1 partner).<sup>40</sup> Thirteen of the 15 partners (92%) given a referral card attended a clinic appointment, but comprised only 15% of all partners. The question is whether treatment rates would have been nearly so high had all the male partners been told to come to the clinic via referral card. The principal reason index women gave for choosing patient-delivered partner therapy was that they were not sure their partners would attend. Finally, time spent with an index patient at the point of care is worthwhile. Although we explore this proposition more clearly in Part III, data in a previous review of male index patients suggested that simply raising the prospects and profile of patient referral produced better partner notification outcomes.<sup>6</sup>

## Hybrid Approaches

As mentioned previously, some countries use a mixture of public health intervention, either through trained staff or third party methods (e.g., physicians) and patient referral for partner notification. A 2005 review of partner notification in European Union countries (and Norway) reveals a variety of systems, all of which rely mostly on patients as the medium of notification.<sup>59</sup> Of the 15 systems surveyed, only 5 offered provider referral and only Norway and Sweden mandated any partner notification for reported STDs. Both countries plus six others (the Netherlands, UK, Denmark, Italy, Ireland, and Austria) had published guidelines for partner notification; interestingly, the presence of guidelines does not appear to correlate with countries' geographic location in Europe, the dominant religious doctrine in the country, or the likelihood of a conservatively or liberally-oriented government. Only Spain among those surveyed had no legal status identified and no guidelines for partner notification. In general, countries with specialty clinics for STD tended to have more developed partner notification programs, and staff in specialty clinics tended to know more than others about partner notification.<sup>59</sup> A scan through the reference section of this chapter will show that these factors are also correlated with the amount of public health partner notification research published in these countries.

In the UK, for many STDs, including syphilis and HIV, the physician or health advisor offers assistance and speaks to the need

to refer partners for care during a post-diagnosis conversation or counseling session.<sup>89,90</sup> In some circumstances, patients may ask the provider to handle notification, but a more typical outcome is that the patient takes responsibility for handling notification and referral. The health agency, however, will follow-up with the patient at 4 weeks, usually by phone. During this follow-up conversation, the health advisor will check to see if the patient has notified the partner, sometimes speaking to the partner then and helping ensure he or she is evaluated or treated. When partner identifying information is taken at any point in this process, the health department or agency can evaluate the efficacy of this hybrid method.

Public health contact with index patients in this manner may well improve program levels of partner management (Table 17.5).<sup>91–98</sup> We examined UK audit data from 8 studies published since 2004, the year in which the British Association for Sexual Health and HIV (BASHH) set up national standards. A ninth study<sup>99</sup> covered partner notification among women with diagnosed PID, but numbers were low ( $n = 30$ ), only one-third had STD etiology, and we could not discern the method of partner notification. Twenty of the 30 patients did have their partners notified and treated.

Overall, the audit data revealed substantial heterogeneity in treatment indices (number partners treated per index patient and an important indicator of effectiveness). The range was 0.12 to 0.97, and the median was 0.49. Syphilis featured at both ends of this range. The highest figure was derived from a sample of 101 patients who were offered provider referral. Of the 102 partners named (a contact index of 1.01), 98 were contacted and tested.<sup>94</sup> The lowest figure was for a Newcastle audit of 41 men with almost exclusively casual and largely untraceable partners for whom it was unclear that provider referral was attempted.<sup>95</sup> The audit actually recorded a notification index of 1.68 (19% of all partners), but only 44 tested. The remaining audits were mostly cases of gonorrhea or chlamydial infection. Thanks to audit standards, partner treatment was more likely to be verified through some sort of personal contact with partners or patients than is typically the case in the US for these STDs. The national audit,<sup>91</sup> as well as a 13-clinic audit from the UK Midlands<sup>92</sup> reported similar treatment indices, 0.41 and 0.49, suggesting that the presence of standards alone does not elevate partner treatment to rates sufficient to stem transmission.

## Program Services and Measurement

Two retrospective evaluations of program data point to the usefulness of public health intervention at the point of diagnosis for HIV. As noted under *Provider referral*, a Seattle study showed that a conversation with a DIS (not necessarily DIS follow-up) improved the odds of notification.<sup>80</sup> An evaluation of New York city data compared the effects of clinical providers attempting to perform partner notification from HIV-infected cases against DIS efforts to do the same.<sup>100</sup> DIS elicited more partners and notified 71% of them, versus 48% for clinical providers. Overall, DIS accounted for 27% of new diagnoses against 22% for clinicians, even though DIS saw 206 index patients against 3460 seen by clinicians. With HIV, US testing services do not always offer

**Table 17.5:** Audit Summaries for UK Partner Notification

Citation for audit	Population, STD and setting	PN intervention	Principal PN outcomes measured	Principal PN findings	Miscellaneous design and analysis considerations
McClean et al. 2008 <i>Int J STD AIDS</i> <sup>91</sup>	5032 cases audited throughout UK 2007	Patients counseled about PN	Documentation of PN counseling; partners tested	4577 91% received PN counseling, CT contacts tested (verified) per index case 0.41	
Manavi et al. 2008 <i>Int J STD AIDS</i> <sup>92</sup>	Audit of 13 West Midlands UK genitourinary clinics 2007	Chart review by clinics with case information reported for 10 index cases each of CT, GC Early Syphilis and HIV	Number of partners identified and treated type of partnership (casual or regular)	632 index patients identified 958 partners 283/311 screened partners (91%) were in regular relationship 647 of partners untraceable (majority casual partners)	
Sawyer & Manavi 2007 <i>Int J STD AIDS</i> <sup>93</sup>	231 GC-infected persons (100 female) UK	Review of case notes of culture positive GC infections; including counseling and contact tracing by health advisors	Partners notified	0.33 partners for each GC cases contacted; 77 partners in total notified and managed w/in 4 weeks; 32/131 (0.24) men and 45/100 (0.45) women	
Fernando & Thompson 2007 <i>Int J STD AIDS</i> <sup>94</sup>	101 patients infected with syphilis; 85 men (73 MSM), 16 women; UK	Patient interviewed for partners, health department assistance offered	Partners elicited, contacted and tested	102 contacts identified; 98/102 (96%) confirmed follow-ups with testing and/or tx	
Chauhan et al. 2006 <i>Int J STD AIDS</i> <sup>95</sup>	40 male GUM clinic patients with early syphilis, Newcastle, UK 2002–2003	Patient interviewed for partners, follow-up not specified	Partners notified, tested, cases found	59 regular partners (41 men); 303 casual partners (293 male). Notification index = 1.68 (19% of partners notified); 44 tested; 22 with reactive serologies	Most partners were male casual contacts, study notes most were untraceable. UK Guidelines indicate provider referral should be used <sup>1</sup>
McClean et al. 2006 <i>Int J STD AIDS</i> <sup>96</sup>	781 syphilis patients, UK national 2004	Patient interviewed for partners (78% health advisor, 19% medical provider); patient versus healthcare-based follow-up not specified	Partners notified, treated	683/781 (87%) of patients interviewed; Contact index = 1.28 (997/781); Treatment index = 0.65 (511/781); 51% of reported partners	UK National Guidelines for syphilis management specify only that the patient and provider should discuss who will notify partners and that both options should be available
Evans & Bacon 2006 <i>Int J STD AIDS</i> <sup>97</sup>	STI clinic patients, London, UK 2000–2002	Patient referral instruction (UK guidelines) <sup>1</sup>	Chart documentation of PN instruction; Partner treatment records	88% patients with documented PN instruction; Partner treatment index = 0.45	PN audit part of more expansive periodic clinical care and follow-up audit
Fernando & Clutterbuck 2005 <i>Int J STD AIDS</i> <sup>98</sup>	189 male CT patients at GUM clinics, Edinburgh, UK 2003	Partner interview, follow-up method not specified	Partners notified and/or treated	Contact index = 0.74 (140 partners). 124 partners (89%) verified as tested or epi-treated	Patient referral with health advisor check on progress is typical of CT partner management in UK

partner services. Of 590 patients responding to a survey in Los Angeles and Chicago, 49% reported the testing agency did not discuss partner notification with them, and 61% did not offer DIS assistance.<sup>101</sup> The figures for medical providers from the same study were 34% and 53%, respectively.

With respect to measurements, the availability of relatively standardized data in the UK has made it plausible to compare services geographically and across time. The US has national-level surveillance data for several STDs, including HIV, and healthcare reform prospects in information technology (e.g., electronic medical

records and reporting) may aid population-level measurement there in the future. Some arguments remain in partner notification around data verification.<sup>102,103</sup> Self-reported figures may well be inflated, but requiring third-party verification of all data limits innovation and scope. At its extreme, the requirement is also prone to tautology (if only DIS can verify outcomes in the field, for example, then only provider referral is evaluable).

Much has been made in other medical settings about the needs for protocols and the people to enforce them (with or without audit standards, one Scottish survey found only 52% of physicians in two

Scottish care centers discussed partner notification with patients).<sup>87</sup> South African program evaluations have shown how a protocol introduced in a medium-resource setting can dramatically improve service delivery.<sup>104</sup> Measurement of current practice is the first step, as shown through a Singapore survey in which only a minority of physicians discussed partner notification, although a majority took sexual histories and gave overall counseling.<sup>105</sup> Similar efforts in Vietnam revealed even less basic knowledge,<sup>106</sup> but the good news is that both surveys documented care and infection control deficits with a view to remedying them.

Two final notes conclude this section. During an audit of Australian data, England and colleagues noted that health department-based partner notification better than doubled the number of partners seen (verified!), but took almost 7 hours per partner.<sup>107</sup> They noted that cost considerations needed to be taken into account alongside efficacy–cost effectiveness is important. Second, this quote from British auditors illustrates how measurements of either effectiveness or cost effectiveness need to speak to outcomes: “Compared with auditing outcomes, audit of management policies overestimated performance in contact tracing...”<sup>96</sup>

### Part III: Innovations in Partner Notification

Innovations in partner notification are often explained in the provider and patient referral terms we have used to categorize practice.<sup>108</sup> This split, however, may reflect a US-centric bias based around the history of the heavily public health investigator-centered syphilis partner notification approach and the modal reliance on patient referral with minimal accompanying intervention for infections such as chlamydial infection. As illustrated in the previous section, partner notification internationally today is performed through collaborative hybrid approaches. In the US, much innovation takes this form, including public and private cooperative efforts.<sup>8</sup> Therefore, we have described innovations into categories that require direct public health involvement *in the notification process*, and those that rely on the patient as the direct means of notification. IPN has provider and patient referral versions, and we have discussed those in a separate section.

#### INNOVATIONS IN PUBLIC HEALTH PARTNER NOTIFICATION PROGRAMS

Even though the principles of interviewing index cases and tracing their partners have been put into practice for decades, there is still room for innovation. Some of the most important innovations come in the form of policy changes. When New York state changed to name-based HIV reporting accompanied by partner notification, many people feared fewer people would get tested. However, testing rates remained stable and more people could then receive partner notification interventions for HIV.<sup>109</sup>

#### Interview Enhancements

Brewer and colleagues tested the concept of memory aids to improve recall of partners through an RCT in the Colorado

Springs STDs program in 2000–2001.<sup>78</sup> Brewer et al. tested 3 enhancements to the routine partner interview: (i) a combination of common locations where people meet partners, relationship roles, network ties and first letters of names; (ii) common first names; and (iii) a list of physical characteristics (the control condition). The first set of enhancements yielded approximately one extra partner per two index patients interviewed, versus approximately one for every four interviewed in the other two conditions. The first condition led to a statistically significant increase in the number of partners located per index patient, compared to the third condition.

Notably, each condition was designed to elicit further partners that the index patient had *forgotten*, that is, there is no presumption of lying or prevarication required. Also, of 55 index patients initially reporting 1 partner who were enrolled in the study in its early stages, only 1 reported a further partner. Therefore enrollment was subsequently constrained to those initially reporting multiple partners. Although a review of the literature revealed no replications in the United States, Brewer’s methods have been replicated in Brazil. Public health staff in an HIV testing facility in Rio de Janeiro used location cues, social roles, the alphabet and demographic cues to stimulate memories of partners not initially recalled by index patients.<sup>110</sup> As with the Colorado Springs population, recall of additional partners was confined to those with multiple partners already named: of those with 2 or more partners, 7% recalled at least one more after staff applied the intervention. Among those with 4 or more partners, the cues yielded additional partners from 18% of index patients.

#### Field-Delivered Therapy

Beyond improvements to interviewing, some programs have tested the effects of giving DIS more tools to use during field investigations. One simple innovation is the practice of taking medications out into the field to administer to notified partners: field-delivered therapy (FDT). In some areas of the United States, public health nurses act as DIS, in which case the partner can receive some sort of clinical evaluation before being offered the medication. Even if this is not the case, however, the field investigator can ask some questions (e.g., about prior medication allergies) and observe the administration of oral single-dose medications, thus ensuring partner treatment. In San Francisco, insufficient rates of partner treatment for gonorrhea and chlamydial infection led program staff to permit DIS to take single-dose medications into the field to give to partners, when located.<sup>111</sup> “Partner packs” included the treatment, instructions, and preventive items such as fact sheets, clinic contact information, and condoms. DIS typically contacted partners by phone and arranged a meeting. At that meeting, the partner could ask questions and take the medication; the DIS could observe for adverse events and provide counseling and education. No further contact was required. Treatment rates rose from 62% of 432 partners assigned to DIS in 1998 (all clinic-based treatment) to 81% of 630 partners in 2000 (67% clinic, 14% FDT), a 31%



increase,  $p < 0.001$ . The increases held broadly across gender, age, and race, with the exception being for MSM, among whom nearly all cases (93%) had been treated in 1998, that is, prior to FDT implementation. A subsequent study from San Francisco incorporating FDT into services for homeless youth found high acceptability and minimal reinfection.<sup>112</sup>

## Network Analysis in Partner Notification

Incorporating social contacts into the partner notification investigations is not a new concept, dating back to instructional manuals for decades.<sup>113</sup> Retrospective analyses of the links among infected persons, their sex (or drug-using) partners, and sundry social contacts has sometimes yielded a more complete portrait of STDs in a given community and provided information useful for public health-mediated partner notification efforts.<sup>114,115</sup> A UK evaluation based on a single HIV-infected person resulted in a network of 123 people, all sex partners or partners of sex partners—15 previously undiagnosed HIV-infected people, 11 previous positive HIV cases, and 4 cases of syphilis.<sup>116</sup> Partner notification was accomplished through a mixture of provider referral (104 cases, 71% success, 55% with known outcomes) and patient referral (19 cases, 79% with known outcomes).

Even more obviously useful are prospective efforts using network techniques, although STD program resources and expertise often make such efforts difficult. One example is an Atlanta syphilis outbreak from the late 1990s, in which DIS performed interviews for partners as per normal practice, but also spent extra time (up to 80% of total hours) in street settings, interviewing index cases and others for drug use partners and important social contacts.<sup>117</sup> These additional contacts were encouraged to seek testing. Forty-eight index patients named 130 partners, of whom 30 were infected, and 153 other contacts, of whom 9 were infected. Contacts of uninfected persons yielded 6 infections from 113 sex partners and social contacts. This 5% prevalence of syphilis is high for a rare disease in the US, and the extra 15 cases generated from the network interviewing added 50% to the 30 cases found through basic provider referral (the yield from provider referral was certainly much higher). A more recent evaluation in British Columbia introduced social network interviews and mapping of cases during a syphilis outbreak.<sup>118</sup> The addition of network information in this investigation showed that more cases were linked to one another (24% vs. 32%,  $p = 0.03$ ), improving public health ability to manage the outbreak.

Network analyses in Atlanta and British Columbia revealed some people who were central to the overall sociosexual network. Such individuals could be interviewed in later outbreaks or even periodically without outbreaks to produce a more efficient series of investigations over time. The process, done well, could also bring community members into the case-finding process, essentially acting with public health rather than as the object of an investigation.

Two final examples show what can be done with patients acting as the agents bringing in social contacts for testing in programs operated by health departments. In Seattle, US, an evaluation

of “patient-driven cluster referral” presented infected persons in STDs clinic the option of referring for testing up to 3 others who they thought would benefit from testing.<sup>119</sup> Those making referrals received a modest amount of cash, as did those who presented for testing. People who referred infected persons could then recruit others, as could those who were tested. The method revealed a 5% rate of previously undiagnosed HIV among those tested, as well as 31% with HCV (excluding known positives) and 8% with gonorrhea. Cost per case of HIV detected was \$4939, compared to over \$11,000 for CBO-based counseling and testing services in the same area and time period.<sup>119</sup> A similar approach with HIV-infected persons recruited through community-based organizations offering HIV testing and referral in several east coast US states yielded a 6% rate of previously undiagnosed HIV among those referred for testing.<sup>120</sup> Although patient-mediated efforts to use network approaches preclude some analyses—not all components can be connected without further interviewing—the method is inexpensive and can be used to complement routine DIS interviews and provider referral (as was the case in Seattle).

## INNOVATIONS NOT REQUIRING DIRECT PUBLIC HEALTH INVOLVEMENT

For the most part, innovations that do not require public health involvement are innovations in patient referral. EPT is probably the most widely known of these innovations in recent years, although certainly not the only novel approach. EPT, which encompasses a series of models in which partners of index cases are offered treatment *without* a prior clinical evaluation. FDT, as discussed above, falls into this category if the field agent is not a clinical provider (e.g., a public health nurse). More often, the index patients bring medications or prescriptions for medication to their partners, most commonly known as patient-delivered partner therapy (PDPT). A hybrid model in the UK is known as accelerated partner therapy (with the felicitous acronym of APT). In APT, health advisors conduct an initial interview with patients and provide options for partners to have some contact with healthcare professionals (phone or pharmacy) before receiving medications.<sup>121</sup>

The goal of the various versions of EPT is to increase the proportion of partners treated, thus curing infection and stemming transmission (including reinfection of the index). One clear sacrifice is the knowledge of whether one is treating an infected partner or treating on a prophylactic basis (epidemiologic treatment). A potential sacrifice is the loss of other information gained in a clinical follow-up: coinfections not treated by the medication administered through PDPT, the opportunity to counsel partners, and the opportunity to ascertain risk factors such as medication allergies. Some of these issues can be obviated in FDT if the field agent is qualified, for example, to assess for allergies. Nevertheless, PDPT in particular needs to be confined to circumstances in which serious adverse reactions to medications are very rare. This is the case with azithromycin (used to treat

chlamydial infection) and the third-generation cephalosporins used to treat gonorrhea—at least in the US and other countries that can afford public health infrastructure. PDPT should also be accompanied by instructions on taking the medication, for corollary care associated with treatment (e.g., for how long to abstain from sexual activity after treatment), and encouragement to seek clinical care.

Between the mid-1990s and 2003, CDC sponsored four RCTs testing EPT efficacy among male and female heterosexual patients infected with chlamydial infection, gonorrhea, and trichomoniasis.<sup>69,122–124</sup> These RCTs have been reviewed on several occasions.<sup>125–127</sup> Here, we emphasize that the RCTs were conducted in several different settings (including six geographically dispersed cities in the first trial), with some variance in operational details. Nevertheless, the principal outcome measure, reinfection in the index patient assigned to EPT relative to patient referral, was quite consistent across trials. For example, the patients in the PDPT arm of the Seattle RCT received prescriptions and were offered DIS assistance; those in the New Orleans urethritis RCT (a majority of which was based on gonorrhea) received medications and counseling.<sup>69,123</sup> The reduction in reinfection (gonorrhea-only in Seattle) in both settings was close to 50%. Seattle and six-city RCT data for chlamydial infection, if expressed as odds ratios, were identical to two decimal places.<sup>69,122</sup>

The strength of EPT, based on US studies, is the robustness of the effects across different settings, at least where gonorrhea and chlamydial infection are concerned. The Seattle RCT in particular also illustrates a point about the value of placing an intervention with a public health goal in a realistic program setting. That is, outside the parameters of a RCT, a patient who asks for DIS assistance in a public clinic should get it; so a trial that includes that programmatic reality has more external validity and more chance of being translated into other STDs programs than one that does not. Research that incorporates program-relevant questions and realities into the actual conduct of efficacy research has more chance of attaining the broader goals of effectiveness and impact: points recently encapsulated in STDs prevention research as “program science.”<sup>128</sup>

The most recent work in the US comes from a second RCT with 484 female index patients, this time comparing PDPT versus DIS-assisted referral versus patient referral.<sup>129</sup> Importantly for estimating reinfection, this RCT included a test of cure at 9 days: 95% of the patients were negative for trichomoniasis at that point. Index patient reinfection rates with 61% follow-up were not significantly different among the arms at one month, ranging from 5.8% (PDPT) to 15.0% (DIS). At 3 months (but only 40% follow-up), the percent positive in those two groups were almost reversed, with 14.3% in the PDPT arm and 7.8% in the DIS arm. Although the 3 month comparisons between groups are confounded by differential treatment rates at 1 month, the reinfection rates (approximately one-sixth of those seen by 90 days) do illustrate how easily people can become reinfected. The authors estimated 34% of partners were treated from those cases they could verify; together with reinfection rates, these data

show how inadequate partner treatment fails to stem infection control in a population.

As the preceding paragraph shows, the large majority of the efficacy research has taken place in the US. The British APT model is tailored to the existing partner management approaches in the UK and contains elements of PDPT, but also FDT.<sup>121</sup> That is, the two APT models currently in UK testing rely on the existing health advisor contact at the time of diagnosis and treatment. The health advisor conducts an interview with the index patient that includes a history of sex partners. In one model, the patient then immediately phones the partners, who speak via telephone with the advisor, who conducts an assessment. The patient can then leave with medications (and an optional self-test kit for gonorrhea and chlamydial infection). The patient also carries instructions for taking medication and a referral for the partner to attend the clinic for further evaluation. The second model has the assessment of partners mediated through pharmacies: the index patient is given a referral card for each partner, and the partner can receive an assessment, medications and a self-test from a local community pharmacist. In both cases, a health professional is able to speak directly to the partner before dispensing medication. In neither case does the partner have to visit a clinic, although the visit to the pharmacist is presumably similar in some costs.

Interviews with 37 patients revealed the options were broadly acceptable and appreciative of the perceived efficiency, with a majority preferring the phone model, as if in the role of the index patient.<sup>121</sup> In the role of the partner, opinion was split. Some barriers raised to the phone call model were related to the potential shock value of the notification: is the partner aware the patient went to the clinic; will the partner have a private place to talk; and a general preference among some patients for personally notifying the partner. Although this last preference is generally positive with respect to successful notification, it essentially nullifies the prospects for APT. Some felt receiving treatment at a pharmacy would be less embarrassing than at a clinic, although others felt it would actually be worse (less private) and thought the pharmacists would not be suitably skilled to deliver counseling. Respondents, however, perceived the pharmacy model as an answer to some of the barriers in the phone call model, so the choice between the two is likely to provide greater coverage and superior prevention impact to having a single model. What is required for APT now is evidence of efficacy, with exploratory trials pursuant to a RCT currently underway.<sup>130</sup>

The spread of EPT in the US continues as an increasingly regulated activity, as opposed to the largely unregulated but widespread use identified in a 1999–2000 national survey.<sup>3,131</sup> Many relevant medical organizations support EPT as an option, including the American Medical Association, Society for Adolescent Medicine, and the American Bar Association. The number of states that either explicitly permit EPT or that appear to have no legal impediments to its practice has risen from 11 in 2005<sup>132</sup> to 21 in late 2009. The number of states with prohibitions (not aimed expressly at EPT, but certainly

applicable) has fallen from 13 to 8. Patient surveys suggest PDPT in particular is acceptable to clinic attendees as a concept,<sup>133–135</sup> although factors such as costs certainly affect uptake.

Nevertheless, EPT, especially as PDPT, faces ongoing operational barriers. Concerns about adverse reactions for patients persist. Because those concerns are typically the first mooted by people who have not considered EPT, the data on the lack of serious adverse reactions to medications is reassuring to many. California and Washington, two states that have maintained several years of efforts to assess serious adverse events through hotlines (phone and e-mail versions), have not recorded one. Other concerns pertain to incomplete care—essentially that partners who receive medication will avoid seeking more comprehensive care. Some skepticism is correlated with institutions' ability to manage partners through other methods. A survey of New York state local health departments showed that health departments with fewer resources to trace partners were more favorably disposed to PDPT.<sup>136</sup> A British survey revealed that 50% (again) of 206 genitourinary medicine physicians surveyed had used PDPT and that two-thirds of physicians were favorably inclined toward using PDPT for chlamydia.<sup>137</sup> However, a much lower proportion (24%) favored PDPT for gonorrhea, and health advisors, who were also surveyed, felt less positively toward PDPT in general (21% had ever used PDPT).

The authors<sup>137</sup> also collected quotes from respondents: these mirrored early concerns advanced in the US, including some views of PDPT as unsafe: "I believe PDPT is unsafe;" as a competitor with other interventions, "It undervalues the role of sexual health interventions including risk reduction strategies;" possibly as a competitor for jobs, "It is a cheaper option to spending money on health advisors;" and as an all-round harbinger of doom, "Do not go down this slippery slope!" Without drawing too firm a conclusion from individual quotes, some respondents appear to construe PDPT as something of a job threat, or as a threat to public health or clinical practice. One notes that the UK has a relatively well-developed and evaluated infrastructure including measuring partner outcomes—in Brazil, attitudes were far more positive, with researchers specifically noting the need for some methods to help control STDs rates with which public health simply could not keep up.<sup>138</sup> Elsewhere, Arthur and co-workers' review of partner notification in Europe<sup>59</sup> showed that EPT (referred to as patient-expedited therapy) was used in approximately half of the countries surveyed, but almost always in less than 10% of cases, and typically only for chlamydial infection. Not that national program responses, as in this survey, are a perfect guide to clinical practice: the flat "No" reported for the UK contrasts against published references to the practice from the same year.<sup>88</sup> The same was true in the US, where responses from state medical and pharmacy boards<sup>139</sup> were uncorrelated with reports of clinical practice.<sup>131</sup> Finally, although neither Greece nor Spain were counted as practicing EPT, antibiotic treatment there was available over the counter in 2005, suggesting that at least some patients brought medications to partners (or the partners got them) without a prescription, let alone a clinical evaluation.

An editorial accompanying Trelle and co-workers' 2007 systematic review<sup>125</sup> specifically named patients' difficulty disclosing (i.e., notifying) partners of their exposure as a key unmet need, and one that required counseling.<sup>140</sup> The point is pertinent, as many patients are asked to notify partners with no tools or counseling around how to do so. Trelle et al.'s analysis covered several counseling and educational interventions with the conclusion that some combination of written and verbal information improved outcomes for patients and partners, although simple randomized comparisons between basic patient referral and patient referral with counseling enhancements were infrequent. One Zimbabwean RCT with an interactive partner notification counseling session demonstrated improved notification rates for men (1.8 partners notified versus 1.2 in the control group), but not women (0.7 in each group).<sup>141</sup>

Theory-based counseling at the time of diagnosis has recently been shown to help reduce reinfection among patients diagnosed with STD in clinics. A US RCT in Brooklyn, New York was designed to test the effect of counseling patients about patient referral on reinfection (with chlamydial infection or gonorrhea).<sup>142</sup> The aims of counseling were to increase the patients' motivation to notify their partners and prepare them with the specific skills to do so, constructs derived from social cognitive theories of behavior that have been applied to sexual risk and STDs prevention before.<sup>143–145</sup> Participants received counseling that included discussion of behaviors that could have led to infection, development of a partner notification plan for each partner identified, role playing exercises, and signature of a contract to execute the plan. Patients took written materials with them, including referral cards and a summary of steps to successful partner notification as discussed with the counselor (nothing wrong with a cheat sheet here!). A second session was designed to take place by phone or in person at a target of 4 weeks from the initial session; this session centered around a progress review and barriers to completion, if any. This second session was similar to the UK structure with counseling and follow-up.

Partner notification rates were high in both RCT conditions (86% control, 92% experimental; OR = 1.8, 95% CI = 1.02–3.0), but reinfection rates, the primary outcome, were substantially lower in the experimental arm (6% vs. 11%; OR = 2.2, 95% CI = 1.1–4.1). The RCT showed larger effects for men than for women, who had higher base rates of notification and therefore less room for increased rates as a group.

One useful point to note for programs considering implementation or replication is that the authors conducted pre-RCT formative research to identify beliefs and opinions among the target population that were salient to partner notification. The principle is applicable to any replication, but the specific salient beliefs might easily differ by locale (especially if one considers international dissemination). For programs with infrastructure including DIS, we note that these staff should be ideal collectors of precisely this formative data. We also note that basing a largely behavioral intervention on sound social science principles is a benefit to the recipients and to public health.



## INTERNET-BASED PARTNER NOTIFICATION (IPN)

With the emergence of nearly every new technology comes the challenge of adopting and adapting it for intervention, including using new technology to reduce infrastructure and service gaps between economically developed and other countries.<sup>146</sup> In the US, the internet as a venue for sex seeking began to draw real attention in the late 1990s.<sup>147</sup> In 2000, the San Francisco City Health Department used e-mail or chat room handles to contact partners of 6 MSM diagnosed with early syphilis.<sup>148</sup> The men named approximately 12 partners per index case, of whom 42% (notification index of 5.9) were located through internet contact. Other studies revealed similar results,<sup>149</sup> confirming that when the only identifying information of an anonymous partner is an e-mail address or screen name, the internet, however tenuous, is the only viable means for reaching these cases for partner notification.

Many health departments recognized the need to adapt traditional DIS activities to the internet, and CDC encouraged health departments to adopt the internet as a tool for partner notification and STDs prevention. CDC also funded the National Coalition of STD Directors (NCSDD) to develop a national set of guidelines for internet-based partner notification<sup>150</sup> and has yet more recently required jurisdictions receiving STD prevention funding to form IPN protocols. To date, approximately half of US states use IPN in some form or another, although bureaucratic obstacles and lack of infrastructure or trained staff continue to pose barriers. Where there are no public health IPN services, partner notification remains the province of patient referral.

A Texas, US study assessed the effectiveness of internet provider referral for 177 partners of 53 men (contact index = 3.34) for whom the DIS had only e-mail addresses, comparing the efficacy to standard provider referral.<sup>17</sup> With e-mail only, DIS notified 50% of partners and were able to bring to treatment 80% of those notified. Provider referral with phone or personal contact was more efficacious, (70% notified and 95% of those notified brought to treatment), so presumably a program would use those methods, if available. However, the grand total of 40% of partners evaluated, a BTI of 1.34, is a good deal better than 0 (the alternative with no protocol). Furthermore, the authors note that use of IPN allowed for rapid communications and required no additional field work or after hour work for staff.

The District of Columbia, US analyzed STDs program disposition codes (the accounting framework for reporting endpoints of case investigations) and found that incorporating IPN into current efforts increased outcome indices including notification, and treatment.<sup>151</sup> Among 286 patients with early syphilis who were interviewed by DIS, 88 (31%) reported a sex partner met via the internet. IPN increased the overall total number of cases investigated by 75%. Indices for new treatment and new exams increased by 22% and 26%. The authors concluded that using the Internet allowed them to notify at least 75% of the internet partners of their STD exposure, allowing them to reach previously untraceable sex partners.

One twist on IPN is to offer an internet-based proxy for the DIS interview. The Houston Health Department offers a confidential, computer-based option to index patients that mimics the typical DIS interview, [www.penshouston.org](http://www.penshouston.org). The health department has partnered with local community-based organizations (CBOs) and private providers to encourage use of the website among syphilis positive patients, in addition to offering the online service to patients resistant to traditional partner notification efforts. To date, no evaluation of the system has been conducted due to a lack of funding.

Patient-based IPN approaches include web-based systems such as InSpot.<sup>18</sup> InSpot began as a response to a San Francisco needs assessment in which respondents (mostly MSM) reported that they would be likely to notify a primary partner of an STD exposure, but less likely to notify casual partners. Additionally, when asked if they would use an anonymous online partner notification system if one were made available to them, many stated that they would. InSpot users log on and choose an electronic postcard (e-card), specify an STD, add a personalized message (if desired) and can send the e-card to up to 6 different e-mail addresses. The user also has the option of sending the e-card anonymously or from a personal e-mail address. In 2006, the designers released an updated version of the website to be used by all audiences.

Currently, anyone in the world can use InSpot for IPN, but various jurisdictions have purchased the system to add local resources. An evaluation of website metrics found that since 2004, over 30,000 users have sent over 45,000 notifications.<sup>18</sup> Fifteen percent of cards were sent for gonorrhea, 15% for syphilis, 12% for chlamydia, and 9% for HIV. The remainder was sent for "other" STDs, including a proportion naming crabs (typically thought to be an indicator of facetious use). Of those receiving an e-card, between 27% and 29% have clicked on the e-card for additional information.

What remains to be seen is whether receipt affects referral rates; that is, does testing follow receipt? A Colorado clinic-based study found little use by largely heterosexual men and women attending clinics (<5%), despite numerous marketing attempts including palm cards, newspaper, radio, and internet ads, few clinic patients had either heard of or used the service.<sup>152</sup> An Australian qualitative study also found internet-based methods less acceptable to heterosexual clinic attendees,<sup>153</sup> with many respondents finding IPN in lieu of in-person notification to be essentially failing a responsibility. These findings tend to be conflated with relationship length and ease of notifying a person directly—both MSM and heterosexual populations are more attentive to personally notifying longer term partners and less so for casual partners.<sup>154</sup> Populations with more causal partners and more internet partners are more likely to use IPN independent of their preferences with primary and casual partners.

Finally, social networks such as MySpace and Facebook have also become avenues for IPN and for improving the outcomes of partner notification in general. Users of social networks often post pictures of themselves online, in addition to other locating information such as city, work or school affiliations and mobile



phone numbers, providing DIS with additional identifying information. Unlike a standard e-mail address, contacting a person via a social networking site typically requires the person conducting IPN to establish a profile on that site. Aside from the well-known social network sites above, sites often used for sex-seeking also have similar requirements. Some sites permit free profiles for public health agents for partner notification purposes, facilitating infection control through collaboration. A profile also allows the notified person to learn something about the DIS and the health services offered.

## Conclusions

The role of partner notification in prevention impact is to get enough partners notified *fast enough* to disrupt networks and stem further transmission. In prevention impact terms,<sup>12,13</sup> this means getting sufficient coverage with a sufficiently efficacious intervention. The third element of prevention impact, the contribution of the population to morbidity may be assumed to be sufficient because the index patients are 100% infected.

We conclude, therefore, with observations about how to ensure that there is enough coverage with enough efficacious interventions, realizing that partner notification is one contribution to the intervention mix. As context for these observations, we note that some experts in partner notification have agitated against the drift of much partner management into various versions of patient referral. In the United States, the federal public health advisor corps had, by the early 2000s, shrunk by approximately 60% compared to the late 1980s, while the number of STDs for which they were responsible had increased dramatically. Personnel and other resource conflicts between managing syphilis and gonorrhea during the early 1990s illustrate this issue. In fact, the core area interview approach in New York state<sup>53</sup> originated as an effort to accommodate the detailing of DIS involved in gonorrhea control to syphilis control efforts. Resources have been a source of stress for a long time: a table footnote in Wigfield's 1972 review reads "the comparable figure [to 502] for 1960 was 242. In 10 years the work has doubled; the staffing is static."<sup>64</sup> Some things never change.

We also note some present issues affecting partner notification have been previous concerns. For example, the current issues with ability to locate partners over the internet mimics the concerns expressed for syphilis partner notification among drug-users in the US epidemic and rise in syphilis during the late 1980s and early 1990s. The authors of an evaluation of partner notification in Oregon concluded that "Because patients infected with syphilis have relatively large numbers of anonymous sexual encounters, prevention strategies that supplement partner notification are urgently needed to control the syphilis epidemic..."<sup>155</sup>

A larger dedicated group of public health advisors would almost certainly help in most countries, whether their first purpose were to introduce protocols, train local staff to perform provider referral, or something else. However, public health agencies have little choice but to accommodate patient-mediated

interventions, and the US is certainly unlikely to return to a time in which, say, most diagnosed gonorrhea is followed up by DIS. Instead, the field needs to continue to stay abreast of factors influencing coverage, including technological innovation (text messaging as a medium of notification), population mobility, forced or voluntary, and, perhaps most important, the ability to ensure some form of partner notification remains a part of STD prevention programs that are integrated with other services. Ten years ago, US national level data showed that a large majority of STDs were diagnosed outside public settings,<sup>156</sup> which necessitates prevention in those same settings. When an efficacious innovation in partner notification (e.g., EPT, brief counseling) is adapted to work in the settings in which STDs are diagnosed, one has moved toward sufficient coverage and sufficient efficacy in an infected population: prevention impact. Whether in the service of reducing disparities in an economy with long-standing public health infrastructure<sup>157</sup> or as part of HIV healthcare in an economy with currently increasing public health capacity,<sup>158</sup> multiple interventions in multiple healthcare settings seems not just the future of partner notification, but increasingly the present.

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# section **iv**

## **PUBLIC HEALTH ASPECTS OF STI CONTROL** — *Graham Neilsen*

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# 18

## Implementation of STI Programs

Gabriela Paz-Bailey • Jerry Owen Jacobson

### Introduction

Close to a million people acquire a sexually transmitted infection (STI), including the human immunodeficiency virus (HIV), every day.<sup>1</sup> In pregnancy, untreated early syphilis will result in a stillbirth rate of 25% and be responsible for 14% of neonatal deaths—an overall perinatal mortality of about 40%. Syphilis prevalence in pregnant women in Africa, for example, ranges from 4% to 15%.<sup>2</sup> The sequelae of STIs include acute symptoms, chronic infection, and serious delayed consequences such as infertility, ectopic pregnancy, cervical cancer, and the untimely deaths of infants and adults. The presence in a person of an STI such as syphilis, chancroidal ulcers, or genital herpes simplex virus infection greatly increases the risk of acquiring or transmitting HIV. Despite this evidence, efforts to control the spread of STI have lost momentum in the past 5 years as the focus has shifted to HIV therapies.<sup>3</sup>

Prevention and control of STIs should be part of comprehensive sexual and reproductive health services in order to contribute towards the attainment of the Millennium Development Goals<sup>4</sup> and respond to the call for improved sexual and reproductive health as defined in the program of action of the United Nations International Conference on Population and Development (Cairo, 1994).<sup>5</sup>

This chapter contains recommendations for the implementation of national STI programs. It covers issues on policy framework, program management and structure, essential components of an STI strategy, and considerations regarding program scale-up.

The first section of this chapter addresses the need for national reproductive and sexual health strategies that provide the organizing framework for policies, laws and programs related to STIs including HIV. It also discusses the importance of integrating sexual and reproductive health and HIV services in different settings and the need to identify and review policies and regulations that hinder access to STI and sexual and reproductive health services. Integration issues are explored in depth in Chapter 19.

The second section discusses the steps needed to develop a strategic plan for a national STI program and to develop health

systems capacity, including situational assessment, determination of program priorities, and design of strategies. The third section deals with STI program components, including methods to promote healthy sexual behavior, protective barrier methods, and effective and accessible care for STIs. STIs occur with the highest frequency among marginalized populations who have unique problems in accessing healthcare services. Securing the level of support to provide effective interventions to these groups is especially challenging, though the public health benefits are substantial. Emphasis in this section is placed on a public health approach based on sound scientific evidence and cost-effectiveness.

The final section examines strategies for overcoming common limiting factors to program scale-up, how scale-up may influence cost and the emerging literature on the impact of expanding specific STI programs on broader health systems.

### Policy Environment

Countries should have a national reproductive and sexual health policy to provide an organizing framework for the development of laws and programs related to STIs including HIV. In turn, national policies should be aligned with internationally agreed-upon reproductive health strategies and aim to contribute to international health targets. WHO's reproductive health strategy rests on internationally recommended instruments and declarations of human rights, including the right of all persons to the highest attainable standard of health; the basic right of all couples and individuals to decide freely and responsibly the number, spacing, and timing of their children and to have the information and means to do so; the right of women to have control over, decide freely and responsibly on, matters related to their sexuality, including sexual and reproductive health, free of coercion, discrimination, and violence; the right of men and women to choose a spouse and to enter into marriage only with their free and full consent; the right of access to relevant health information; and the right of everyone to enjoy the benefits of scientific progress and its applications. In order to ensure that

these rights are respected, policies, programs, and interventions must promote gender equality, and give priority to poor and underserved populations and population groups.<sup>3</sup>

National policies and programs should also contemplate how best to link sexual and reproductive health, STI and HIV services in different settings.<sup>3</sup> While evidence that well-designed HIV responses can and do strengthen health systems is encouraging,<sup>4</sup> nonetheless, evidence suggests that greater and more systematic efforts must be made to take HIV responses out of isolation to support wider health, development and human rights agendas.<sup>6</sup> There are several linkages among HIV, STI, sexual and reproductive health responses. For example, services to virtually eliminate mother-to-child HIV transmission provide an ideal platform to deliver the recommended minimum package of antenatal, maternal, child and reproductive health services. Such services would ensure that pregnant women are not only offered HIV screening, but that they and their partners are also offered services to prevent acquisition of HIV and other STIs, unintended pregnancies and sexual violence.<sup>6–8</sup> Interventions to control STIs in family planning clinics, antenatal and maternal and child health clinics would further expand opportunities for prevention, detection, treatment and thus STI control.<sup>3,9–11</sup> For further reading the United Nations Population Fund (UNFPA) has produced guidelines and recommendations on how to improve linkages between sexual and reproductive health and HIV.<sup>12–18</sup>

Calls for integration of HIV services with reproductive health services are not new. Global consensus in this respect was reached as early as 1994 with the International Conference on Population and Development's Program of Action<sup>5</sup> and has been repeatedly reaffirmed in subsequent global declarations, notably the United Nations Political Declaration on HIV/AIDS of 2006.<sup>3</sup> Such political commitments have provided motivation on a programmatic level to take the HIV response out of isolation. Thus, HIV initiatives such as the International Health Partnership, President Obama's Global Health Initiative, the United States President's Emergency Plan for AIDS Relief, the joint approach of the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the World Bank and the GAVI Alliance now support actions toward sustainable and cost-effective health systems more generally.<sup>11</sup> As international HIV strategies adopt a broader health-strengthening perspective, it remains imperative to renew the commitment to controlling all STIs. National STI programs, in turn, should incorporate evidence-based public health policies for treatment and prevention, emphasizing effective integration of sexual and reproductive health services with HIV services.<sup>10</sup>

When evaluating the policy framework it is important to consider that, in some countries, laws, policies, and regulations can serve as obstacles to effective STI program provision. For example, they may hinder access to services (e.g., laws governing sex work, homosexuality, or drug use), limit the roles of health personnel (e.g., preventing nurses from performing HIV testing), bar services (e.g., restrict access to STI and family planning services for adolescents) or restrict the importation of essential

drugs and technologies. STI program managers should identify and advocate for improvement of laws or policies that result in restricted access to, or reduce the effectiveness of, STI prevention and control efforts (Box 18.1).<sup>19</sup> Elimination of unnecessary restrictions from policies and regulations and steps toward creating a supportive framework for reproductive and sexual health are likely to contribute significantly to improved access to services. Regulations are needed to ensure that commodities (medicines, equipment and supplies) are made available on a consistent and equitable basis and that they meet international quality standards. In addition, an effective regulatory environment is needed to ensure public and private sector accountability for providing high-quality care for the entire population.<sup>10</sup>

As a precursor to advocating for policy changes, common misconceptions regarding STI programs must often be dispelled before certain issues can be included in the policy agenda.<sup>7</sup> For example, curriculum-based sex education does not increase risky sexual behavior as many fear, and trends towards early and premarital sex are neither as pronounced nor as prevalent as some believe.<sup>20</sup> On the contrary, systematic reviews have shown that school-based sex education can lead to improved

#### Box 18.1 Policy Environment

##### Resources for STI prevention and treatment

- Budget allocations for STI treatment relative to other diseases.
- Private sector commitment to STI care.
- Provision of the recommended antibiotics to public sector clinics and inclusion of effective antibiotics on essential drug lists.

##### Restrictive policies and procedures

###### Women

- Policies that restrict access to services and require a husband's permission for examinations, intake of drugs or use of barrier methods.

###### Youth

- Policies that restrict access to clinical services for STI and family planning.
- Policies that restrict access to condoms.

##### Condoms and STI drugs

- Tariffs that make importation costly and cumbersome.
- Restrictions on distribution of condoms to minors or unmarried women.

##### Service access

- Restrictive laws that prohibit diagnosis and treatment of STIs by non-medical health personnel, decreasing access to services.
- Policies that encourage clinic-based, laboratory-dependent and physician-managed STI services exclusively.

##### Human rights

- Laws that push risk behavior "underground" or make it hard to communicate with vulnerable people.
- Laws that permit or encourage discrimination against people living with HIV.
- Laws that increase vulnerability to infection or its consequences, including those relating to imprisonment.
- Constitutional or national principles that reinforce or contradict commitments made in international agreements.

Note: Adapted from Dallabetta G, Laga M, Lamptey PR, eds. *Control of Sexually Transmitted Diseases, A Handbook for the Design and Management of Programs*. 1st ed. Arlington, VA; 2001.

### Box 18.2 Evidence of Educational Policies on Abstinence and STI Rates in the United States

A recent study in the United States evaluated the relationships between state-leveled educational policies and STI rates. The authors analyzed US case reports of gonorrhea and chlamydial infection for 2001–2005 against state policies for abstinence coverage in sexuality education. They also tested for effects on 15–19 year olds versus 35–39 year olds and tuberculosis rates, to ensure findings applied only to STI. States with no mandates for abstinence had the lowest mean rates of infection among the overall population and among adolescents. States with mandates emphasizing abstinence had the highest rates; states with mandates to cover (but not emphasize) abstinence fell in between. These effects were not shown for tuberculosis. The authors conclude that having no abstinence education policy has no apparent effect on STI rates for adolescents. For states with elevated rates, policies emphasizing abstinence show no benefit.<sup>92</sup>

awareness of risk, knowledge of risk reduction strategies, increased self-effectiveness, intention to adopt safer sex behaviors,<sup>21</sup> and to delay, rather than hasten, the onset of sexual activity. It is also important to recognize that some sexual and reproductive health policies have been adopted in the absence of sufficient evidence or even in contradiction to the evidence. One example is the widespread promotion of abstinence-only programs, which employ prevention strategies for which evidence has not been established, while restricting the use of proven ones (Box 18.2).<sup>20</sup> In such instances, NGOs and civil-society groups, in collaboration with the research community, have a responsibility to advocate for policies founded upon evidence of impact rather than ideology. Strong advocacy and leadership are needed at the global and country level to provide clear messages about the importance of controlling sexually transmitted and other reproductive tract infections, identify the interventions and programs that work, identify the constituencies that affect resource allocation, and create multidisciplinary coalitions to advise decision-makers.<sup>2</sup>

## Program Management and Structure

To be effective, STI control programs must be tailored to the national and local epidemiological situation as well as relevant behavioral and cultural patterns. Consequently, no standard STI program will be appropriate for every country; even within a single country, an STI control program must change over time to adapt to changes in the epidemiological context and societal conditions.<sup>23</sup> Yet, even if STI programs differ in operational detail, their objectives and the requirements for an adequate management structure are inevitably similar.<sup>19</sup>

The objectives of STI control include the following:

- Interrupt the transmission of STIs;
- Prevent the development of diseases, complications, and sequelae; and
- Reduce the incidence of HIV infection.

An STI control program seeks to achieve these objectives through a management structure that delivers both communication efforts and clinical services to treat and prevent infections. Preventing

infections involves promoting sexual and reproductive health, safer sexual behavior including condom use, and assuring that high-quality, affordable male and female condoms are available. Treatment involves promoting healthcare-seeking behavior, particularly among those at increased risk of acquiring STIs, and providing accessible, acceptable and effective diagnosis and management for symptomatic and asymptomatic STI patients and their partners.<sup>10</sup>

Because the activities required for the control of HIV overlap with those required for the control of STIs, it is essential either that HIV and STI programs are fully integrated or, if independent, that there is coordinated planning and integration of selected activities. This will ensure effectiveness of both programs and will minimize duplication of effort and wastage of scarce resources. Areas for coordination or integration include care and treatment, advocacy, health education and counseling, promotion of safer sexual behavior, provision of condoms, surveillance, program evaluation and resource allocation. One way to achieve coordination is through a single manager for both programs with authority to coordinate overlapping functions. Those areas relating most specifically to STIs, such as case management, can be undertaken by a second level of management supervised by an HIV/STI manager.<sup>23</sup> The STI program should interact with other programs at the Ministry of Health and with health workers at various levels of the healthcare system, both in the public and private sectors. Collaborations should be established with medical associations, training institutions, non-governmental organizations (NGOs) and the business sector. It is particularly important to coordinate with primary healthcare, maternal and child health, and family planning programs.<sup>19</sup>

Program implementation should be decentralized as much as possible. However, there are some common functions that may be carried out by an STI management unit (e.g., in the national Ministry of Health) or otherwise coordinated to assure consistency and coherence nationally. The responsibilities that need to be coordinated at the national level include: (i) designing strategies and setting priorities; (ii) planning and supervising control activities; (iii) coordinating resources and activities within the program, and with other programs or sectors of the healthcare system, both public and private; (iv) defining case management guidelines and ensuring availability of commodities such as medications; (v) ensuring functioning of the surveillance system and identifying operational research priorities; and (vi) monitoring, supervising, evaluating, and revising the control program or planning its expansion.<sup>19</sup>

## INTEGRATION OF STI SERVICES INTO PRIMARY HEALTHCARE SYSTEMS

The experience of health programs other than STI control suggests recommendations for the introduction of STI care and prevention into general national healthcare systems:

- Integration of an STI package with a broader health structure makes sense only when the existing primary



healthcare structure functions reasonably well, providing favorable conditions for incorporating new STI services. Where a health district functions reasonably well, the chances are that integration of an STI package will go smoothly, produce results, and provide a model and motivation for other districts.

- The STI package should be as simple as possible so that it can be easily incorporated into health facilities' routine activities with minimal disruption, thus minimizing resistance from staff.
- Begin by integrating the STI prevention and care package. Once routine STI prevention and care is functioning, it is possible to move on to the second stage, with specific activities directed at partner notification and treatment, outreach to high-risk core groups, etc.
- Devise a concrete strategy to overcome likely sources of resistance that are likely to be encountered, particularly in contexts of work overload and low salaries, which may act as constraining factors. Two common types of resistance are:
  - Resistance by health workers based on fear of the unknown, prejudice and reluctance to take on further responsibilities (e.g., health education and skills development must start with healthcare workers);
  - Resistance by STI specialists based on a fear of reduced quality and loss of their power position. This can often be overcome by demonstrating the usefulness and possibilities of decentralization, as by providing specialists with a clear task description that respects their role and status in the new system (e.g., referral, quality control, training, operational research, and surveillance).
- Incorporate a system of monitoring and supervision of STI care and prevention services from the very beginning.

Any development of specialized structures such as referral laboratories or dedicated STI clinics should meet the following criteria:

- The tasks to be performed by specialized structures are essential and cannot be undertaken by existing or by upgrading existing facilities;
- No new needs should be addressed before the basic established needs are met;
- Investments in the specialized structures do not come at the expense of the support required to integrate STI care in the general health services;
- The specialized structures will exhibit comparative advantage both in the short- and long-term.

Experience suggests that, if such criteria are not met, specialized structures will divert resources meant for the strengthening of the primary healthcare network and it becomes difficult to dismantle even when proven ineffective, inefficient, or counterproductive.<sup>23</sup>

## PROGRAM PLANNING

Strategic planning is the process of defining a strategy or direction for an organization and making decisions on allocating its resources to pursue this strategy. The strategic plan orients the program over the next 3–5 years, defining goals in the specified time frame. In order to set its goals, the organization needs to assess its current situation, determine where it wants to be and how it will get there.

Planning and implementing STI control activities involve several phases: (i) conducting a situational analysis; (ii) securing political commitment; developing a national sexual and reproductive health policy including STIs and HIV; (iii) setting program priorities; (iv) designing objectives and strategies; (v) developing a work plan for implementation and support components; and (vi) mobilizing resources, and implementing a monitoring and evaluation strategy.

## Situational Analysis

A situational analysis examines the current circumstances relevant to STIs and, in particular, the factors that favor or impede STI transmission and acquisition. It thus helps to identify opportunities for change to the status quo. The analysis exercise also provides an opportunity to build partnerships across the public sector and among the public, private, and community groups in society, bringing a wide range of people, skills, and resources into the national response.

During a country's first situational analysis exercise, the government should try to involve as many *key* stakeholders as possible, not only to increase diversity and expertise, but also to create a sense of ownership among involved agencies. This involvement is also crucial for resource mobilization. Bilateral donors or international NGOs are often keen to participate in the different phases of the strategic planning process. It is also important to involve the community and representatives from the most affected populations such as people living with HIV, sex workers, and men who have sex with men.<sup>24</sup>

The situational analysis should include a description of STI epidemiology, existing services, available resources, and influential factors (political, cultural, legal, and other) (Box 18.3). The outcome therefore is not a mere description of the STI epidemiological status in the country; it is a diagnosis of the major underlying determinants and an identification of groups or populations most vulnerable to STIs. In the process, the team also pinpoints the major obstacles to, and potential opportunities for, improving the situation and strengthening the response. It thus paves the way for developing the most appropriate strategies. Box 18.3 lists the main questions to be addressed in the situational analysis.

## Political Commitment

However good the available technologies and interventions, they will be of no sustainable benefit to the population without the



**Box 18.3** STI Situational Analysis**Objective:**

To understand the current STI status and what can be done to improve it.

**Main Questions:**

- What is the STI situation in the country or a particular area?
  - Epidemiology and clinical syndromes, STI pathogens and their antibiotic sensitivities;
  - Type and size of populations at greatest risk.
- What major factors and risk behaviors are associated with STIs?
- Which are the existing services, public sector and private sector, including physicians, other healthcare workers providing STI services, pharmacies and unqualified healthcare providers?
- What is the STI healthcare-seeking behavior among the general population and high-risk and vulnerable groups?
- Which political, legal, and social factors that may influence the national (or local) program?
  - Positive or negative political commitment.
  - Legal constraints:
    - Registration of sex workers and/or establishments;
    - Availability of antibiotics without prescription.
- What are the priority areas that need to be addressed now and in the short and medium term?
- What obstacles are there to improvement or change in priority areas?
- What opportunities are there for positive changes?
- What are the available resources:
  - Allocation of funds from the Ministry of Health (or local authority);
  - Available personnel;
  - Infrastructure, equipment, materials, consumables;
  - Availability of and funding for drugs;
  - Resources for study, operational research, curriculum development (university clinic, medical schools, social studies and educational institutions, etc.);
  - Actual/potential additional resources (such as international agencies, donors, NGOs);
  - Availability and commitment of other healthcare programs/services that can deliver STI care (such as reproductive health programs).

**Means:**

- Key informant interviews:
  - Ministry, district, and local officials;
  - Healthcare providers;
  - NGO staff;
  - General and target populations.
- Documents:
  - Reports, laws, and regulations;
  - HIV plans;
  - Health facility and laboratory records;
  - Publications and internal reports from local and national government offices, NGOs, donors and neighboring countries (areas);
  - Visits and observation.

Note: Adapted from Lamprey PR, Gayle HD, eds. *HIV/AIDS Prevention Care Resource-Constrained Settings, A Handbook for the Design and Management of Programs*. 1st Ed. Arlington, VA; 2001.

political will and resources to continue their implementation. In most countries, it is difficult to promote safer sexual behaviors and introduce sex education into school curricula without the due level of political commitment. Advocacy must occur at both the country and global levels to put STI control high on the national

health agenda. Furthermore, strong leadership supported by civil society, a clear vision, messages, strategies, and interventions with a solid science base is required to inspire action. At the country level, advocacy should promote enabling policies and legislation. Existing regulations and legislation should be reviewed to assess their utility and contribution to prevention and care policy, goals and objectives relating to STIs. Consideration should be given to reforming policies and legislation that obstruct the goals of prevention and care.<sup>10</sup> As discussed above, a national reproductive and sexual health policy is essential in each country.

### Select Program Priorities

The situational analysis identifies the most important STI determinants and weaknesses in the response, and recommends focus areas for a new strategic plan. Through situational analysis, each country will identify its own priority areas for action. Countries must implement or scale up the provision of care for those with STI through activities for which there is sufficient knowledge and evidence of impact and feasibility. The World Health Organization drafted a Global Strategy for STI Control that outlines a series of activities that may serve as guidance. Table 18.1 describes these activities, together with indicators and national targets.<sup>3</sup> Priority 1 activities are interventions that have been implemented in many places with modest additional human and financial resources. Priority 2 activities are interventions that may require substantial human and financial resources, and plans should be made for stepwise implementation as resources become available.

### Design Objectives and Strategies

The general objectives of an STI control program delineate the program's expected achievements. Specific objectives detail accomplishments for a given period of time, and steps toward achieving the program's larger objectives. They should be formulated including the expected outcomes, target populations and geographic areas or socioeconomic levels, and the timeframe for reaching the stated outcomes. The target is usually expressed as a proportion of the population for which a specific outcome is expected. For example: 90% of STI patients attending public facilities in the capital city will be managed according to national diagnostic and treatment guidelines by the end of year two.

A set of activities undertaken to meet a specific objective constitutes a strategy. One or more strategies may be implemented to meet an objective. The relationship between specific objectives, strategies and activities is illustrated in Box 18.4, while examples of activities, indicators and targets are listed in Table 18.1.

### Designing Strategies

At a minimum, strategies need to be designed for the following program components:

1. Behavior change strategies to promote safer sexual behavior, consistent and correct condom use, and appropriate

### Box 18.4 Example of Objectives, Strategies, and Activities for STI Program Priorities

#### Objective

By the end of the year 3500 female sex workers and 3000 men who have sex with men in the capital city will have been reached with an evidence-based behavioral change intervention for high-risk groups.

#### Strategy

Network based behavioral change intervention

#### Activities

- Estimate the size of the population of female sex workers and men who have sex with men in the capital city.
- Organize a prevention committee with organizations working on prevention with high-risk groups.
- Develop access to target groups through key members.
- Develop a work plan to coordinate activities.
- Train health providers and peer educators in outreach activities.
- Develop a reporting mechanism.
- Monitor activities.

healthcare-seeking behavior – including efforts directed at reducing stigma and discrimination;

2. Delivery of services for management of STI patients and their partners;
3. Condom programming.

These components must be implemented in a coordinated fashion. For example, if the behavioral change communication recommends early treatment of STIs, then such services should be available. Similarly, if the use of condoms is promoted, they should be accessible. These and other components of an STI program are discussed in more detail in the next section of this chapter.

### Work Plan for Implementation and Support Components

After defining program priorities and strategies, the program manager must prepare a plan for implementing control activities. Close coordination with the essential drugs program is a key to ensuring availability of appropriate STI drugs at primary healthcare facilities. If the strategic plan involves providing STI case management for women through maternal and child health, family planning and antenatal clinics, these programs should be involved early in the planning process. Available financial, human and physical resources must be considered when planning STI control to avoid constraints imposed by resource shortages. For example, limited funds for training staff in syndromic management will mean that program activities cannot be implemented countrywide. It is often necessary to adopt a phased approach to program implementation. For example, a program could initially develop interventions in one or more urban areas where high-risk behavior is common and STI incidence is high. Simultaneously, additional research on the etiology of STI syndromes and on antibiotic susceptibility patterns could begin. In a later phase, services could be expanded to other urban settings and to rural areas as well. Preparation of

a step-by-step work plan with a realistic timetable and budget is a crucial step in program planning.<sup>19</sup>

The following support components are essential to developing and implementing an STI control program and should be included in the detailed work plan:

- Guidelines;
- Training;
- Clinical mentoring and supportive supervision;
- Logistics (including drugs and condoms);
- Laboratory services;
- Research;
- Surveillance;
- Monitoring and evaluation for the program.

These components are discussed in more detail in other sections of this chapter.

### Mobilize Resources

In order to implement the strategy, a mechanism to mobilize additional resources will likely be needed. For developing or resource-limited countries, various sources can be explored. For example, countries may take advantage of the opportunity to develop proposals for the Global Fund to Fight AIDS, Tuberculosis and Malaria that include strategies for STI control. At the global level, international agencies should intensify discussions on funding for STI control through such mechanisms. There are also other opportunities, such as foundations interested in STI control in general or for specific populations. At the national level, advocacy strategies for adequate resource allocation for programming for the prevention and control of STIs should be developed.<sup>25</sup>

### Essential Components of an STI Control Strategy

The three main objectives of an STI control program (interruption of transmission of STIs, prevent development of disease, reduce incidence of HIV), along with the three core intervention strategies (behavior change, management of STIs, condom programming), have been discussed in the previous section of this chapter. Additional strategies that may be considered include control of congenital syphilis and treatment and prevention of neonatal conjunctivitis. For effective implementation of these strategies, a number of support activities need to be developed. These include development of guidelines, training, supervision, logistics, laboratory services, research, surveillance, and program monitoring and evaluation. Other support components that are usually outside the direct influence of an STI control program consist of commodities procurement and distribution systems for drugs, condoms and laboratory supplies; a health education unit that supplements and reinforces in-clinic messages for behavioral change and appropriate healthcare-seeking behavior and a health statistics unit to process and analyze surveillance data.

National guidelines for patient management and STI treatment must be developed and widely disseminated. This will facilitate the development of training materials and programs. Specification

**Table 18.1:** Summary of Actionable Interventions for Immediate Implementation

Priority 1 activities	Indicators	National targets
1. Scale-up of services for diagnosis and treatment of STIs (use syndromic management where diagnostic resources are limited)	1(a). Proportion of primary point-of-care sites providing comprehensive case management for symptomatic infections 1(b). Proportion of patients with STIs at selected health facilities who are appropriately diagnosed, treated and counseled according to national guidelines	1(a). 90% of primary point-of-care sites provide comprehensive care for people with STIs by 2015 1(b). By 2015, 90% of women and men with STIs at healthcare facilities are appropriately diagnosed, treated, and counseled
2. Control congenital syphilis as a step towards elimination	2(a). Proportion of pregnant women aged 15–24 years attending antenatal clinics that are screened for syphilis 2(b). Proportion of pregnant women aged 15–24 years attending antenatal clinics seropositive for syphilis that are adequately treated	2(a). More than 90% of first-time antenatal clinic attendees aged 15–24 years screened for syphilis 2(b). More than 90% of women seropositive for syphilis treated adequately by 2015
3. Scale up STI prevention strategies and programs for HIV-positive persons	3. Proportion of primary point-of-care sites that provide effective care to HIV-positive patients with STIs including advice on condom use and partner notification	3(a). Strategies and guidelines on interventions for HIV-positive patients with STIs in place by 2015 3(b). 90% of primary point-of-care sites provide effective care to HIV-infected patients with STIs
4. Upgrade surveillance of STIs within the context of second-generation HIV surveillance	4(a). Number of prevalence studies regularly conducted (at sentinel sites or in sentinel populations) every 3 to 5 years 4(b). Annual incidence of reported STIs (syndromic or etiological reporting)	4(a). At least two rounds of prevalence surveys conducted by 2015 4(b). Routine reporting of STIs established and sustained over at least 5 consecutive years by 2015
5. Control bacterial genital ulcer disease	5(a). Proportion of confirmed cases of bacterial etiology among patients with genital ulcerative diseases 5(b). Percentage of pregnant women aged 15–24 years attending antenatal clinics with a positive serology for syphilis	5(a). Zero cases of chancroid identified in patients with genital ulcer disease by 2015. 5(b). Less than 2% of positive syphilis serology among antenatal clinic attendees aged 15–24 years
6. Implement targeted interventions in high-risk and vulnerable populations	6(a). Health needs identified and national plans for control of STIs, including HIV, for key high-risk and vulnerable populations developed and implemented 6(b). Proportion of young people (aged 15–24 years) with infections that were detected during diagnostic testing for STIs	6(a). By 2015, health needs, policies, legislation, and regulations reviewed; plans in place and appropriately selected country-specific targeted interventions implemented 6(b). At least two rounds of prevalence surveys conducted among groups with high-risk behavior and among young people by 2015
Priority 2 activities	Indicators	National targets
7. Implement age-appropriate comprehensive sexual health education and services	7. Percentage of schools with at least one teacher who can provide life-skills-based education about prevention of HIV and other STIs	7(a). Review of policies and development of age appropriate training and information materials for schools completed by 2015 7(b). Increased number of teachers trained in participatory life-skills-based HIV education that includes other STIs by 2015
8. Promote partner treatment and prevention of re-infection.	8. Proportion of patients with STIs whose partner(s) are referred for treatment	8(a). Plans and support materials for partner notification developed, and healthcare provider training in place by 2015 8(b). The proportion of patients who bring in, or provide treatment to, their partner(s) doubled by 2015
9. Support roll-out of effective vaccines (against hepatitis B and human papillomavirus and, potentially, herpes simplex virus type 2 infections)	9(a). Policy and plans for universal immunization against hepatitis B 9(b). Plans and policy reviews and strategies for use of human papillomavirus and potential herpes simplex virus type 2 vaccines	9(a). Plans in place regarding immunization against hepatitis B and human papillomavirus infection by 2015 9(b). Pilot immunization programs initiated and scaling up in progress by 2015
10. Facilitate development and implementation of universal opt-out voluntary counseling and testing for HIV among patients with STIs	10. Proportion of patients assessed for STIs who are routinely counseled and offered confidential testing for HIV	10(a). HIV testing and counseling available in all settings providing care for people with STIs by 2015 10(b). The proportion of patients with STIs who receive voluntary counseling and testing for HIV doubled

Note: Adapted from World Health Organization. Global strategy for the prevention and control of sexually transmitted infections: 2006–2015: breaking the chain of transmission. Geneva, Switzerland; 2007.

of selected recommended essential STI treatments will simplify STI drug logistics and monitoring of antimicrobial sensitivity. Obtaining broad consensus is an essential aspect of national policy and guidelines development.

We now turn to the core elements of an STI control program strategy in detail.

## BEHAVIOR CHANGE

An effective response to the spread of STI starts with accurate and explicit information on safer sex, including correct and consistent use of male and female condoms, delay in onset of sexual activity, keeping to one, ideally uninfected, sexual partner or reducing the number of sexual partners. A behavior-change strategy should be an integral component of prevention efforts and incorporated into care and support activities. It can increase knowledge of HIV and STI prevention, stimulate dialogue within the community, promote essential changes in attitudes, reduce stigmatization and discrimination, create demand for information and healthcare services, advocate for appropriate policies and laws and improve skills and self-esteem.<sup>26</sup>

When choosing the communication channels for sexual behavior-change messages, it is important to know which can most effectively reach the target population. One successful channel for targeted interventions is through peer educators and opinion leaders. Informational sessions on health through institutional or interpersonal networks, group discussions, or other one-to-one approaches have also been used. Age-appropriate school-based programs help in reaching young people, but for the out-of-school population, other channels, such as peer education, are necessary. Whatever channel of communication is chosen, it is important to use language that is well understood by the target population. Care should be taken that the messages are sensitive to gender and culture and that they do not reinforce any existing norms driving the spread of STIs.<sup>3</sup>

Health education about STIs and counseling of both infected and uninfected people, inclusive for HIV testing, should be an integral part of any health service, as the counseling process creates motivation to change sexual behavior in both infected and uninfected individuals. Education and counseling messages should also highlight the need for sexual partners to be informed and treated properly to avoid repeated infections.<sup>3,19,27</sup>

Development and strengthening the provision of STI care needs to be accompanied by the education of potential service users on the availability and advantages of the services. This should take into account the reasons why many individuals fail to seek early treatment. Some may not seek treatment for the STI, but receive a diagnosis when they attend a medical service for another unrelated condition. Innovative strategies to increase demand for high-quality services should be used. These may include: market-oriented methods for raising consumer awareness of correct, high-quality treatment to be expected from care providers; education for youth in- and out-of-school; education

in health facility waiting areas; education as part of the STI consultation; and peer education initiatives in the community. This approach relies on appropriate changes in the supply of healthcare services to meet increasing demand. Creating high expectations that are not met can be detrimental to continuing service utilization.

## STI CASE MANAGEMENT

Prompt and effective STI treatment is an essential component of STI control. Comprehensive management involves prompt diagnosis and treatment, together with education and counseling of patients on treatment compliance and risk reduction, partner notification and provision of condoms. Several factors interfere with effective STI case management. These include a large number of asymptomatic infections in women, inadequately trained and judgmental health providers, the lack of appropriate diagnostic tests and the lack of effective drugs.

## Syndromic Management

The greatest deficiency in individual case management in resource-poor settings is the scarcity of affordable and accurate diagnostic tests. Syndromic management remains the core intervention in the WHO strategy for delivering prevention and care for people with STIs in resource-poor settings where laboratory testing is not available.<sup>3</sup> Syndromic management involves the use of flowcharts to help healthcare workers identify groups of symptoms and easily recognizable signs (syndromes) and guide treatment to cover the most probable causes of the syndrome.<sup>22</sup> Syndromic treatment of patients at the first visit avoids loss to follow-up and provides an opportunity for education, advice on sexual behavior, promotion or provision of condoms and partner notification. The syndromic approach, which can be used at all levels of healthcare,<sup>28</sup> treats mixed infections, and prospective studies provide some evidence of effectiveness in the management of symptomatic urethritis and epididymitis in men and genital ulcer disease in both women and men.<sup>29</sup> In recent years, HSV type 2 has emerged as the most common cause of genital ulcer disease.<sup>30</sup> WHO guidelines now recommend incorporation of acyclovir into the syndromic treatment package for genital ulcers under specific circumstances.<sup>22</sup>

The syndromic flowchart for the management of vaginal discharge is inadequate for controlling STIs in women because this symptom is a poor proxy for endocervical chlamydia and gonorrhea.<sup>31</sup> Sensitivity and specificity remain low even when supplemented by speculum examination and risk assessment.<sup>29,32</sup> Even in settings where the prevalence of endocervical infections is above 15%, fewer than one in three women diagnosed syndromically will have an STI.<sup>28</sup> Since syndromic management is not appropriate for cervical infections, the use of flowcharts for vaginal discharge has been suggested to provide treatment for vaginal STI trichomoniasis and endogenous reproductive tract infections (bacterial vaginosis and candidiasis).<sup>28,32</sup>



### Box 18.5 Problems with the Management, Use, and Distribution of Drugs for STI Treatment

- Available drugs are ineffective due to the development of antimicrobial resistance.
- Effective drugs for STIs are available only in the private sector (subject to additional taxes), and thus unaffordable to a vast majority of STI patients.
- Effective drugs are not included on the national essential drug lists.
- Healthcare providers continue to prescribe drugs to which the organisms have developed resistance despite the availability of alternatives.
- Pharmacists sell drugs over the counter in doses lower than those recommended when the customer cannot afford to buy the full, recommended dose.
- Out-of-date, counterfeit or inactive drugs.
- Drug vendors sell drugs that are ineffective and/or inadequate.
- Practices that result in ineffective therapy include polypharmacy, whereby several antibiotics with overlapping effects as well as unnecessary creams or ointments are prescribed, resulting in increased cost to the patient as well as unreasonable demands on the patient's ability to remember and comply with instructions.
- Inadequate or nonexistent patient education regarding the prescribed drug, and instructions about how, when and for how long to take it, result in poor patient compliance with the required treatment.
- Patients' difficulty in remembering to take several doses of a pill a day for several days; providers should try to prescribe the drug that requires the fewest doses for the shortest possible period of time and with the fewest side effects.

## Drugs

The availability of effective drugs is crucial for successful STI management, yet it is a problem in many countries. Box 18.5 details several major problems related to the availability of effective drugs that, unless resolved, may reduce the effectiveness of STI prevention and control efforts. The evolution of antimicrobial resistance has made the treatment of gonorrhea and chancroid more complicated and expensive.<sup>33,34</sup> A monitoring system for detecting antimicrobial resistant STI strains and treatment failures is therefore fundamental to procuring more effective drugs and updating providers about current recommendations.<sup>33,35,36</sup>

## Partner Management

Partner notification aims to prevent onward transmission of infection and, if successful, can also prevent re-infection of the index case. Partner notification is a process that includes informing sexual partners of their infection, administering epidemiological treatment and providing advice about the prevention of future infection.<sup>27</sup> Partners can be informed by the patient (patient referral), the health professional (provider referral), or by the health professional if the patient has not done so within an agreed time (contract or conditional referral). In practice, patient referral is the most commonly used, and is the preferred method.<sup>37</sup> A range of partner notification approaches can increase the numbers of sexual partners treated for gonorrhea, chlamydia, syphilis, HIV, trichomoniasis, and STI syndromes, though only a proxy outcome that assumes that partner treatment prevents onward

spread.<sup>37–40</sup> Recent trials have shown that the risk of re-infection or persistent infection in index cases can also be reduced. When compared with basic patient referral, four trials in which index cases received antibiotics or prescriptions to give directly to their partner(s) (patient-delivered partner therapy) showed a reduced risk of reinfection with gonorrhea or chlamydia.<sup>40</sup> For transmission to be interrupted in the population, enough partners of index cases, and their partners, have to be traced and treated for the intervention to have an effect.<sup>41</sup>

## Periodic Presumptive Treatment

*Presumptive treatment* is defined as one-time treatment for a presumed infection in a person, or a group of people, at high risk of infection. Presumptive treatment for STIs is often given at regular, repeated intervals, in which case it is known as *periodic presumptive treatment*.<sup>42</sup> In theory, this approach should reach a greater proportion of people with STIs than treating only those with symptoms, and avoids the costs of diagnostic tests. The interval between treatments must, however, be short enough to deal with reinfection.<sup>43</sup> In Rakai, Uganda, treatment at 10-month intervals had little effect on transmission in the general population, with a reduction in long-term syphilis reactivity and trichomonal infections but no effect on gonorrhea, chlamydia, bacterial vaginosis, or reports of urethral discharge, vaginal discharge, or genital ulcers.<sup>44</sup> The reductions in infection were outweighed by the operational requirements of implementation. Presumptive treatment has been recommended as a temporary strategy to reduce prevalence as part of a package of services in populations known to have very high prevalence of STIs while other curative and preventive services are being strengthened. In female sex workers given monthly single-dose antibiotics in Benin, Ghana,<sup>42</sup> and Kenya,<sup>45</sup> however, only one of three randomized controlled trials, in Kenya, showed a reduction in chlamydia and gonorrhea. The intervention had no effect on HIV acquisition. A program administering periodic presumptive treatment to female sex workers based within geographically self-contained mining communities in South Africa,<sup>46</sup> for instance, found that prevalences of gonococcal and chlamydial infections declined in the women following the intervention. Among the miners in the area, both the rates of genital ulcer disease and urethral discharge also fell sharply suggesting a flow-on population impact in a client group whom did not receive any intervention. Chancroid, which had been the leading genital ulcer among both miners and sex workers at the beginning of the program, was effectively eliminated. Periodic presumptive treatment has not been assessed in other groups—e.g., men who have sex with men, male sex workers, clients of sex workers.

## PROMOTION OF CONDOMS AND OTHER BARRIER METHODS

The male latex condom is the single most efficient technology available to reduce the sexual transmission of HIV and other STIs. Although the female condom is effective and safe, use remains limited by its relatively high cost and variable acceptability among both healthcare providers and potential users.

Male and female condoms and water-based lubricants are a key component of comprehensive prevention strategies, and all should be made readily and consistently available to all those who need them in order to reduce risks of sexual exposure to STIs including HIV. Once procured, condoms should be promoted and distributed through both the public and private sectors, in clinical and non-clinical settings. Maternal and child health as well as family planning clinics are good additional outlets for condom distribution, increasing accessibility to women who could be at risk of STIs. A recent meta-analysis has shown that structural-level interventions aiming to increase the availability, accessibility, and acceptability of condoms are effective in increasing condom use, condom acquisition or condom carrying, promoting delayed sexual initiation or abstinence among youth, and reducing incident STIs.<sup>47</sup> Condom distribution programs were also efficacious in increasing condom use among a wide range of populations including youth, sex workers, adult males, STI clinic patients, and populations in high-risk areas. Program managers interested in implementing a condom distribution strategy should consider the following elements<sup>48</sup>:

- Provide condoms free-of-charge.
- Conduct wide-scale distribution.
- Implement a social marketing campaign to promote condom use (by increasing awareness of condom benefits and normalizing condom use within communities).
- Conduct both promotion and distribution activities at the individual, organizational, and community levels.
- Target: (i) individuals at high risk, (ii) venues frequented by high-risk individuals, (iii) communities at greater risk for HIV infection, especially those marginalized by social, economic or other structural conditions, or (iv) the general population within jurisdictions with high HIV incidence.
- Supplement the condom distribution program with more intense risk-reduction interventions or other prevention or health services for individuals at highest risk. Integrate condom distribution program activities with other community-level intervention approaches to promote condom use and other risk reduction behaviors.
- Conduct community-wide mobilization efforts to support and encourage condom use and address misleading anti-condom messaging by moralizing influential community leaders.

It is also important when launching a condom distribution program to identify and engage appropriate community partners, identify obstacles in reaching members of vulnerable populations and strategies to overcome them. There should be an evaluation of program costs to determine the largest feasible scale. Laws and policies that may support or hinder the program should be identified.

Developing linkages to NGO-managed community-based distribution of condoms and condom social marketing programs can expand the condom promotion efforts. Condom social marketing programs combine vastly expanded condom accessibility with consumer-friendly promotion. These programs sell brand-name condoms through a wide variety of sales points,

including traditional chemist and small retail shops and a myriad of nontraditional outlets, such as bars, hotels, restaurants, market stalls, sidewalk vendors, brothels, kiosks, taxis, and boat launches. Programs around the world have demonstrated that making condoms available at an affordable price in places convenient to users can result in staggering condom sales.<sup>19</sup> In addition to greatly expanding access to condoms through traditional and nontraditional sales outlets, condom social marketing programs have demonstrated a unique ability to diminish social taboos surrounding condom use through their innovative use of both conventional and nonconventional advertising, comedy, street theater, promotional items, and other techniques for changing attitudes. These strategies have served to reposition condoms in the minds of members of target audiences. As a result, the condom is no longer viewed as foreign, sterile medical technology, but rather as a simple consumer product that is easy to use, effective, and increasingly popular.<sup>49</sup>

Other barrier methods such as the diaphragm and microbicides have showed mixed results. A randomized controlled trial failed to show any protection with diaphragms for HIV transmission or STIs.<sup>50</sup> However, among consistent diaphragm users there was some protection for gonorrhea infection.<sup>51</sup> Recent studies evaluating microbicides have shown promising results with some protection of microbicides against HIV although the mechanisms applied are unlikely to prevent bacterial STIs.<sup>52</sup>

## CONTROL OF CONGENITAL SYPHILIS AND NEONATAL CONJUNCTIVITIS

When STIs affect pregnant women, fetuses and newborn infants can also become infected, potentially leading to infant morbidity and mortality. Antenatal screening programs are good examples of interventions that use efficacious single interventions—e.g., diagnostic tests and antibiotics—but for which effectiveness in prevention of transmission is dependent on delivering them in an organized, sustainable way, and in a receptive environment. Intramuscular penicillin for pregnant women with syphilis is effective in preventing congenital syphilis.<sup>53</sup> Because of the high prevalence in developing countries of gonorrhea and chlamydial infections, and the consequent risk of newborn children developing gonococcal or chlamydial ophthalmia, routine prophylactic treatment for such ophthalmia at birth is recommended.<sup>37</sup>

## INTERVENTIONS FOCUSED ON CORE GROUPS

In some geographical settings, rates of STIs in the general population are high, while in others, high rates are confined to specific population groups. Exercises that map infection levels, sexual behaviors (e.g., number of sexual partners and rates of partner change), preventive behaviors (e.g., correct and consistent condom use), and health-related behaviors (e.g., STI treatment-seeking) in population groups with high rates of infection and in vulnerable groups, as well as in the general population, provide valuable information on the transmission

**Box 18.6****Populations at Highest Risk of HIV and Other STIs in Different Settings**

- Sex workers (female, male, and transgendered) and their clients have sex with their regular partners.
- Mobile populations such as long-distance truck drivers, fishermen, seafarers, and migrant workers at increased risk of infection primarily because of their mobility and high-risk sexual contacts.
- Men who have sex with men and transgender women who have multiple sexual partners and engage in unprotected anal intercourse.
- Men who have sex with men as well as women.
- Substance users, especially those who also sell or exchange sex to support their habit or who have sex with non-users.
- Incarcerated persons, especially juveniles.
- External, internal refugees and displaced persons.
- Members of the uniformed services, including military and police.
- Tourists, especially recreational sex tourists.
- Women or men who experience sexual and gender-based violence.
- Children and young people on the street, and those who are abused or are orphans.
- Adolescents at special risk of STIs including HIV, due to lack of the information, skills, healthcare and support needed while going through sexual development.

dynamics and help to determine which interventions for control would be most successful. Targeted interventions should be prioritized according to the needs, feasibility, and availability of resources. The populations vary among regions and countries. Those frequently observed to be in need of targeted interventions are listed in Box 18.6.

## OTHER SUPPORT COMPONENTS

### Supervision

Supervision is a two-way process by which the manager observes and keeps in touch with events, which enables the staff to give feedback, discuss and be reassured and supported. Regular supervisory and monitoring visits to health facilities are an important component of ensuring the continued provision of good quality care and sustaining provider morale and motivation. Such supervisory visits need not be confined to the public sector. They can be adapted to the private sector to maintain quality, provide continuing education, and serve as a means of collaboration between the private and the public sectors.<sup>3</sup> Supervisory visits need to adopt a facilitation process in order not to be a threat to the healthcare providers or other staff, but rather a source of encouragement, and a means of updating healthcare providers and constantly improving quality of care. A supervisory program also needs to be contemplated for outreach workers who are the key to improve access to hard-to-reach populations. Training of supervisors is important, so that they can reorient their skills to being supportive rather than judgemental and fault-finding. Laboratories providing STI support also benefit from supervision of logistics, services, and laboratory investigation.

### Training

Training is a key component of any STI control program. Program managers at the national and local levels need training in the planning and management of STI programs. This involves the development of skills in situational assessment, prioritization and resource allocation, a good understanding of public health measures for STI control and the need to collaborate with and involve different partners in the public and private sectors. Service providers including outreach workers need to be trained in effective case management, education and communication on sex, sexuality, STI and HIV, prevention, condom use, treatment adherence, partner notification, and the development of nonjudgmental and open attitudes. Laboratory technicians may require refresher training in the use of STI diagnostics.

For training to be effective and achieve optimal use of limited resources, training must be needs-based, skills-oriented and targeted to the specific audience. Thus, the skills required by a particular group of healthcare workers or program managers should be carefully defined and training needs carefully assessed.

### Laboratory Services

Depending on the size of the country, it is important that one or more laboratories be prepared to conduct the essential epidemiological and microbiological research necessary for surveillance efforts. Where possible, laboratory tests with a short turnaround time should be available to assist in treatment decisions, particularly in cases that are unresponsive to the first course of treatment. The laboratory can play an essential role in epidemiological and microbiological surveys, antimicrobial susceptibility studies and in the validation of treatment and management approaches. Laboratories should be established and strengthened at national and regional levels and, where feasible, laboratory support can be established at the local level. Such a network of laboratories can work together to strengthen services. To be cost-effective, the network should identify clear roles and areas of responsibility as recommended in Box 18.7.

### Monitoring and Evaluation

It is easy to understand the imperative of assuring that funded initiatives work as expected and succeed in achieving the intended results toward STI control and quality-of-life improvements. Even when resources are plentiful, good program functioning and impact are desirable. Monitoring and evaluation (M&E) systems provide data and analysis regarding program functioning and results to guide decision-making and are an essential component of all health services and interventions. Yet, despite important achievements, M&E continues to be regarded as one of the weakest components of STI programming, so that evidence to guide programmatic decisions is often unavailable or inadequate. The Global Fund to Fight AIDS, Tuberculosis and Malaria recommends that programs spend 5% to 10% of funds on M&E systems.<sup>54</sup> M&E of STI activities should address the coverage,



### Box 18.7 Laboratory Roles and Responsibilities at Different Levels of the Health System

#### National level

- Conducting epidemiological, sentinel, and etiological surveys to monitor disease trends and effectiveness of interventions.
- Validating and adapting flowcharts for recommendations and guidelines for syndromic management.
- Establishing national proficiency and quality control systems for the laboratory diagnosis of STIs.
- Providing training workshops for laboratory diagnosis of STIs.
- Evaluating performance and cost-effectiveness of new diagnostic tests.
- Collating data on antimicrobial susceptibility patterns and making recommendations.
- At referral centers, establishing diagnoses in cases that fail syndromic case management and for medico-legal purposes (e.g., rape or sexual abuse).
- Initiating or strengthening screening programs for asymptomatic gonococcal and chlamydial infections, especially among target populations such as sexually active young women and men.

#### Regional level

- Conducting etiological surveys to monitor disease trends and effectiveness of interventions.
- Monitoring patterns of antimicrobial susceptibility.
- Supporting regional proficiency and quality control systems for the laboratory diagnosis of STIs.
- Providing training workshops for laboratory diagnosis of STIs.

#### Local level

- Supporting sentinel surveys.
- Providing routine serological testing for syphilis in pregnant women.
- At referral centers, establishing diagnoses in cases that fail syndromic case management.

**Note:** Adapted from World Health Organization. Global strategy for the prevention and control of sexually transmitted diseases: 2006-2015: breaking the chain of transmission. Geneva, Switzerland: World Health Organization; 2006.

quality and effectiveness of all STI services provided, including laboratory services. Monitoring and evaluation processes for STI programs are further discussed in Chapter 20.

## Operational Research

Closely related to evaluation is operations or operational research (distinct from the mathematical science concerned with optimal decision-making of the same name).<sup>55</sup> In M&E, operational research refers to any research undertaken to understand and improve program implementation or to identify new areas where interventions are needed. Notably, decision science tools from classical operational research, such as cost-effectiveness analysis, may form a part of M&E efforts. The Global Fund to Fight AIDS, Tuberculosis and Malaria defines operational research as follows<sup>56</sup>:

*“Any research producing practically-usable knowledge (evidence, findings, information, etc.) which can improve program implementation (e.g., effectiveness, efficiency, quality, access, scale-up, sustainability) regardless of the type of research (design, methodology, approach) falls within the boundaries of operations research.”*

As defined above, process and impact evaluation would be considered a kind of operational research. Operational research may involve embedding trials or studies within projects to fine-tune implementation<sup>57</sup> and may use rapid assessment or social science research tools, such as direct observation, interviews, focus groups or surveys of staff or program participants. For example, operational research efforts in Cambodia sought to better understand TB management in the private sector through interviews with doctors, pharmacists, pharmacy staff and patients, as well as using “mystery clients” posing as patients. In this instance, the research identified areas in need of improvement for TB management in private sector facilities.<sup>54</sup>

## Surveillance

Data from STI surveillance systems, correctly implemented and used, serve a number of public health functions:

- To detect cases and case clusters to guide interventions where infection is occurring;
- To support evaluations of determinants of infection and impact;
- To determine the need for public health interventions;
- To monitor the effectiveness of prevention and control measures;
- To develop hypotheses to guide studies of risk factors and causes of infection and disease progression.

Additionally, surveillance systems should place special emphasis on detecting and understanding new infections and behavioral patterns to anticipate how STI epidemics may evolve over time.<sup>58</sup>

*Second-Generation Surveillance* is concerned with both biological (e.g., prevalence and incidence) and behavioral information to characterize and track risk behaviors and contextual determinants that elevate vulnerability to infection (e.g., migration or refugee status leading to increased risk of sexual assault). Second-generation surveillance has primarily an HIV focus but is also relevant for surveillance of other STIs. WHO-UNAIDS guidelines for *Second-Generation Surveillance* in HIV recommend several surveillance components: routine surveillance based on case reporting of HIV, AIDS, and other STIs; behavioral and biological surveillance studies in most-at-risk populations; population size estimation of most-at-risk populations to support projections; and regular analysis to maximize data utilization.<sup>59</sup> The frequency and extent to which these components are required will depend on the type of epidemic.

Surveillance studies in most-at-risk populations for HIV increasingly incorporate estimation of HIV incidence, although methodological problems exist,<sup>60</sup> as well as genotyping to estimate levels of primary resistance of HIV to antiretroviral medications. Surveillance studies that use probability sampling techniques in most-at-risk populations may also incorporate estimation of population size at lower cost compared to size estimation outside the context of a surveillance study.<sup>61</sup> Generally, studies for surveillance purposes should assure adequate representativeness



of target populations to enable statistically valid comparisons between geographic locations and over time.

## Considerations for Scaling Up STI Programs

A common challenge to STI programs in achieving a significant health impact is that of “scaling up”, or dramatically expanding services so that they are universally available.<sup>62</sup> The challenge of scale-up however, is not just one of funding levels. Understanding why efforts to make proven, effective health strategies—such as routine antenatal screening to prevent congenital syphilis—widely available often fail is a nebulous affair, although common reasons include limited health systems capacity, political will and cultural acceptability. A conceptual framework for understanding constraints to scale-up was put forward by the Commission on Macroeconomics and Health, which was convened by the World Health Organization, and concerned primarily with “priority” health interventions that it considered promising toward meeting economic development and equity objectives, including those targeting HIV and other STIs.<sup>62</sup> Constraints were classified according to organizational-institutional level and their likely responsiveness to increased funding. The Commission’s work proposes that those constraints deemed most amenable to improvement through additional funds are those that operate at the community and household levels (lack of demand for services and barriers to utilization), health services level (staffing, management and supervision, supplies, equipment and health infrastructure) and some at the cross-cutting public policy level (communication and transport infrastructure). Constraints seen as largely unchangeable or requiring strategies beyond resources alone occurred at the level of policies, management, and national context (e.g., government bureaucracy and corruption, political stability and security, political will and geographic disposition to disease).<sup>63</sup>

### Box 18.8

#### Strategies for Improving Health System Performance for Scale-up

- Community participation approaches that are highly collaborative.
- Quality assurance, especially via participatory approaches.
- Strengthening management capacity.
- Training programs provided they are:
  - Regular rather than intermittent;
  - Adaptive to changes in the health situation;
  - Linked with supervision.
- Integrated drug policies, including selection, procurement, distribution, prescription and patient education.
- Promoting health services in underserved groups.
- Innovatively addressing bureaucratic barriers.
- Focused objectives, monitoring systems, and good technical design.

**Note:** Based on Seshadri S. Constraints to scaling-up health programmes: a comparative study of two Indian states. *Journal of International Development* 2003;15:101–14; and Wyss K, Moto D, Callewaert B. Constraints to scaling-up health related interventions: the case of Chad, Central Africa. *Journal of International Development* 2003;15:87–100.

Strategies that tend to be effective in overcoming common barriers to scale-up were identified in a review<sup>3</sup> and three country case studies applying the constraints framework, which build on the Commission’s work (Box 18.8).<sup>64–66</sup> Although what works inevitably depends upon the particular intervention and local context, a finding uniform across programs examined is the importance of highly collaborative strategies that utilize community participation to promote or deliver services. Other elements linked with success in scale-up included incorporating efforts to strengthen management capacity, developing quality assurance mechanisms that use participatory approaches, and introducing training programs, particularly when training is linked with supervision, integrated within standing health processes, and designed to be responsive to changes in the health situation. Similarly, an India case study examining programs designed to strengthen HIV control, nutrition and health services found that monitoring systems, focused objectives, good technical design and measures aimed at addressing bureaucratic barriers were all crucial to enabling effective scale-up,<sup>64</sup> while a Chad case study found that a strategy of promoting services in underserved groups was critical in permitting rapid scale-up to occur.<sup>65</sup> Together, the case studies suggest that a failure to address policy and infrastructure constraints can limit possibilities to expand the reach of health services.<sup>65,66</sup>

## “3 × 5” AND ART

The push to provide access to HIV antiretroviral therapy (ART) in low- and middle-income countries, principally in sub-Saharan Africa, is perhaps the most extensive international health scale-up effort in recent history. In December, 2003, WHO with UNAIDS announced an initiative to address the HIV treatment “health emergency”, which aimed to expand ART to 3 million people in developing countries by the end of 2005, equivalent to achieving 50% coverage of individuals requiring treatment in low- and middle-income countries.<sup>67</sup> The 3x5 target was seen as a necessary midway point on the way to achieving universal access to those in need of treatment. It was estimated to require US\$5.5 billion in funding from national and international sources and was considered feasible by WHO.<sup>67</sup>

Although by December, 2005, less than half of 3x5’s desired scale-up had been achieved, large initiatives by the World Bank, the U.S. President’s Emergency Program for AIDS Relief, the Global Fund to Fight AIDS, Tuberculosis and Malaria and other national and international aid organizations succeeded in rapidly expanding ART coverage from about 7% to 20% (from an estimated 0.4 to 1.3 million individuals) in the 2-year timeframe.<sup>67</sup> In 2005 alone, ART coverage nearly doubled globally. The rapid expansion in HIV treatment resulted in part from supply-side changes: large price reductions through increased supply of generics; fixed-dose combination tablets; and discounts from research and development-based companies. Private sector companies, such as Uganda’s Nile Breweries and the Bank of Uganda contributed by offering free ART to their employees. Infrastructure improvements, including laboratory strengthening, were also considerable. The initiatives also

provided substantial investments in training in medical and management areas, including procurement and procurement systems, distribution of medications and supplies, and demand forecasting—all seen as crucial given the relatively high cost of ARV medications and the importance of high levels of patient adherence to avoid treatment failure and the development of resistance. In many African countries, training programs utilized community volunteers and were led in part by universities and NGOs, which facilitated expansion of home-based treatment and alleviated pressure on health facilities.<sup>68,69</sup>

Why then did the 3x5 scale-up initiative, despite such large and varied international investments, fail to meet its objectives? An independent evaluation of WHO's contribution to the initiative produces conclusions that, in retrospect, were to a large extent foreshadowed by the earlier findings of WHO's own Commission on Macroeconomics and Health and related cases studies regarding barriers to scale-up, released close to 3x5's commencement.<sup>67</sup> WHO's evaluation and others<sup>68,69</sup> concluded that more than any other factor, weaknesses in the health systems of targeted countries, in particular human resources for health ("health services level" constraints in the Commission's framework), were responsible for the slower than expected progress. In fact, such constraints had also been signaled midway through the initiative as a likely obstacle to reaching the 3 million coverage goal.<sup>70,71</sup> Underlying the human resources constraints was the systemic and chronic problem of low pay for health workers with access to higher-paying foreign labor markets ("brain drain") and difficulty in deploying medical personnel to facilitate scale-up in rural areas.<sup>68,69</sup> While the Commission cited community involvement as the factor viewed as most critical to health improvement efforts,<sup>72</sup> the 3x5 evaluation suggested that a lack of participation by civil society, especially people with HIV, had slowed ART scale-up in some countries. Similarly, the evaluation cited a failure by WHO to focus objectives and establish an effective program structure in its support role to countries to achieve the 3x5 goal,<sup>67</sup> thus echoing problems detected by the 2003 India case study.<sup>64</sup>

Notably, health services level constraints continue to be viewed as the foremost obstacle to achieving universal access beyond 3x5, with commentators pointing to recurring costs of laboratory equipment and infrastructure maintenance, the need to train and expand the health workforce to avoid negatively affecting healthcare provision outside of HIV; WHO has also recognized the need to distribute and decentralize the ART provision tasks to communities and community health workers.<sup>68,69</sup>

## RAPID TESTS AND SCALING UP SYPHILIS SCREENING

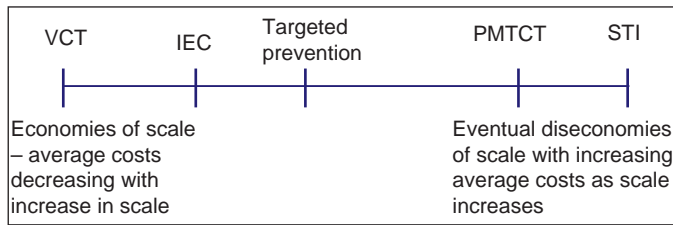
As a second example, the recent availability of a rapid, on-site treponemal test for syphilis with high levels of specificity and, to a lesser degree sensitivity, has been viewed as an opportunity for worldwide scale-up of routine antenatal syphilis screening and treatment.<sup>73–75</sup> Even in countries with low population prevalence, the cost-effectiveness of antenatal screening in preventing congenital syphilis has been established and it may also be cost-saving.<sup>76</sup> Yet, although such evidence and the diagnostic and treatment tools to

prevent mother-to-child transmission of syphilis have been available for decades, universal access to antenatal screening, prophylaxis and treatment has proved an elusive goal, with continuing annual incidence of congenital syphilis estimated at between 713,600 and 1,575,000 cases worldwide.<sup>2</sup>

Availability of on-site rapid tests might also facilitate regular screening and treatment of risk populations by permitting testing beyond the clinical setting.<sup>73</sup> In China, as in a number of countries, national guidelines recommend screening for individuals engaged in sexual risk behaviors, but who do not typically access public health services. Tucker and colleagues<sup>77</sup> discuss the prospects for scale-up of syphilis screening in this context. They emphasize the importance of the availability of evidence of an accelerating epidemic and a responsive government policy environment. However, community, household and health services level constraints remain: assuring appropriate incentives for providers to conduct testing in China's market-based health system and determining who will pay; human resources capacity to conduct screening; stimulating patient demand for testing; determining patient preferences (e.g., finger-prick vs. venous blood testing); organizational structures to permit increased diagnosis, referral and treatment; and establishing cost-effectiveness. While the main advantage of on-site rapid tests is enabling testing in settings that lack laboratory capacity, cost-effectiveness has also been examined, with mixed results to date. For antenatal syphilis screening compared to traditional tests (RPR, VDRL) rapid on-site tests are estimated to be cost-effective in sub-Saharan Africa<sup>78</sup> and Haiti,<sup>79</sup> but not in Tanzania.<sup>74</sup> Compared to VDRL, screening using on-site rapid tests among patients at STI clinics in sex work locations in Manaus, Brazil was not cost-effective.<sup>80</sup> In these contexts, scale-up will therefore depend on willingness to pay the incremental cost of the logistical convenience of rapid versus traditional testing methods.

## SCALE-UP COSTS

As STI programs consider the prospect of expanding, they must project costs at different scales, or service levels to support programming. Yet, evidence remains limited as to how costs change as STI program coverage increases. As one would expect from economic theory, variations in scale across programs tend to explain a considerable portion of variation in cost; for example, in HIV interventions, this share has been estimated at 26–70%.<sup>81</sup> Programs such as voluntary counseling and HIV testing (VCT) with relatively low fixed costs, tend to achieve economies of scale as volume increases and thus a reduced average cost, while the few available studies for other kinds of programs—such as targeted prevention and STI management—have been mixed, some exhibiting economies of scale and others facing reduced costs up to an optimal size, then increasing as resource inputs (e.g., physical infrastructure, personnel) become scarce.<sup>81</sup> Based on fixed costs alone, it is predicted that treatment and prevention of mother-to-child transmission programs (high infrastructure costs) face diseconomies of scale, while expansion of VCT and information, education and communication interventions (low fixed costs)



**Fig. 18.1:** Predicted effect of scale on cost for HIV interventions. IEC: Information, education, and communication; PMTCT: prevention of mother-to-child transmission; STI: treatment of sexually transmitted infections; VCT: voluntary counseling and testing. Reproduced from Kumaranayake L. The economics of scaling up: cost estimation for HIV/AIDS interventions. *AIDS* 2008;22:S23.

would achieve reductions in average cost (Fig. 18.1).<sup>81</sup> An analysis of the first 2 years of the large Indian AIDS Initiative, Avahan, with total costs of US\$16.8 million and reaching more than 134,000 sex workers and clients in 62 districts of four southern Indian states, documented a significant reduction in average cost as well as a 61% share of cost variation explained by differences in scale across the 107 NGOs involved in implementation.<sup>82</sup> However, the analysis did not report how cost responded to scale by each of the different components (education, information, and communication, condom distribution, syringe exchange, STI treatment, and structural interventions). Overall, empirical evidence is limited in this area and STI programs can contribute much-needed information by routinely tracking data on costs and reporting economic analyses.<sup>81</sup>

### BROADER EFFECTS OF SCALE-UP

The immense investment to expand HIV programming in recent years has given rise to a continuing debate regarding the overall impact of these efforts on controlling the HIV pandemic and on health systems. It has been suggested that the relatively greater focus on expanding treatment relative to prevention, coupled with the rapid influx of considerable financial resources for treatment in resource-limited countries, has drawn many community-based organizations away from community mobilization and HIV prevention,<sup>68</sup> even as new infections have continued to outpace the number of individuals commencing treatment by a ratio of 2.5:1.<sup>83–85</sup> At the level of health systems, there is concern that the international focus on HIV has diminished resources available for other health priorities.<sup>86–89</sup> Others contend that HIV investments benefit the health system overall.<sup>90</sup> With little evidence available regarding these issues, the *Bellagio HIV/Health Systems Working Group* has recently proposed a research agenda to improve understanding of the impact of HIV scale-up on various aspects of health systems, with an emphasis on orienting “vertical” versus “horizontal” approaches to incorporating HIV within the health sector.<sup>91</sup>

## Conclusions

This chapter has outlined essential aspects of STI program implementation. The main conclusions from this chapter include:

- Countries need a reproductive and sexual health national strategy that serves as a framework for policies, laws, and programs related to STIs including HIV. It is important that the policy framework and the organization of programs provide ways to best link sexual and reproductive health, and STI and HIV services in different settings. Removal of unnecessary restrictions from policies and regulations, in order to create a supportive framework for reproductive and sexual health, is likely to contribute significantly to improved access to services.
- Managers of STI control programs are responsible for ensuring that program resources—human, material or financial—are used in the most cost-effective way to reach the program’s stated objectives. To fulfill this responsibility, managers must assess the available resources, the infrastructure and the extent of the STI problem. They must prioritize the strategies and activities that are most likely to achieve the program’s objectives cost-effectively. Carrying out these strategies and activities requires a detailed work plan with a realistic timeline and budget. A work plan’s implementation must be monitored against set targets, and an evaluation will reveal how successful the program has been in reaching its stated objectives.
- The three main objectives of an STI control program are: interruption of the transmission of STIs; prevention of the development of diseases, complications and sequelae; and reducing the incidence of HIV infection. These can be achieved by a combination of the following core interventions strategies: (i) Behavior change strategies to promote safer sexual behavior, consistent and correct condom use, and appropriate healthcare-seeking behavior; (ii) Delivery of services for management of STI patients and their partners; and (iii) Condom programming.
- STI programs face constraints beyond funding when attempting to scale-up. Important lessons have been distilled from systematic reviews of health development work and specifically with respect to HIV interventions such as WHO’s 3x5 effort. Chief among these are the importance of community participation strategies, sufficiently addressing limitations on health capacity, focusing objectives and implementing well-planned and coordinated participative monitoring and supervision mechanisms. Thoughtful review of why past scale-up efforts have met with success or failure and learning from this experience should be part and parcel of any new scale-up initiative. As average costs may increase or decline as operations expand, all scale-up attempts should include detailed cost forecasting to anticipate changes. The impact of large investments in specific STI strategies—such as HIV treatment—on service provision in other health areas remains poorly understood; all STI programs should seek to achieve synergies to strengthen the overall health system.



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# Integrating STI Prevention, Care, and Treatment with Other Sexual and Reproductive Health Services

Kathryn Church

# 19

## Introduction

There are a variety of possible ways that health programs can scale-up access to STI prevention, care, and treatment. In various settings, STI programs target high-risk populations with little attention paid to bringing services to the wider community. In these contexts, care may be delivered through specialist STI units or centers, or through specialist outreach programs aiming to deliver care to specific groups, such as sex workers. In settings of rising community STI prevalence, integration of STI prevention, screening and treatment into primary care or with other types of health services offers an important strategy to broaden service scope and scale-up access and coverage. Integration of services can also be a more cost-effective and efficient way of delivering healthcare than vertical programs.

Integrating healthcare entails actions at both service-delivery and policy levels. At the service-delivery level, a range of service modalities are possible to integrate STI care, including one-stop shops offering comprehensive sexual and reproductive health (SRH) care, comprehensive primary healthcare (PHC) which includes STI services, semi-specialist STI providers or units within larger health services, or effective referral models to specialist care. The specific service modality chosen will depend on a range of factors, including the level of care that is being provided (i.e., whether outreach, primary, secondary, or tertiary), the population being served (including the specific local STI epidemiology), the pre-existing structures and infrastructure of the health system and the human resource capacity to deliver STI care.

The capacity to deliver integrated services also depends on the degree of intersectoral collaboration among health programs. Within national or state-level health programs, STI services have historically fallen under the remit of a range of different departments, including SRH, HIV, and/or communicable diseases. Integrating policy and programmatic components may therefore be a prerequisite to integrating services.

This chapter will discuss how integrated services are currently being considered within the sphere of public health, with a focus on health systems in low- and middle-income countries

(LMICs). It will start with a discussion on the meaning of integrated services, and how understanding models of integration are crucial for quality STI programming. It will then give an overview of the history of shifts between vertical and integrated health programs, and the reasons for these trends. It will further discuss the current drive and rationale for more integrated models of care, focusing particularly on STIs and other SRH services. It will then outline the specific models of integrated services being considered, including integration into SRH services, as well as bringing SRH care into more vertical STI and HIV services. Lastly, it will discuss specific challenges to integration and strategies to overcome them.

## Vertical and Integrated Approaches in Healthcare

### A SHORT HISTORY

Current public health debate on integrated services has been strongly influenced by a recent history of oscillations between what have been described as “vertical” health programs, and more “horizontal” or integrated approaches. Vertical or “disease-specific” programs result from political decisions that recognize the importance of specific health problems based on epidemiological, economic, social, cultural, or political criteria.<sup>1</sup> They derive from vertical analyses, which see one health problem as independent of others, and are associated with a more medicalized model of infectious disease control.<sup>2</sup> Vertical approaches have been successful in controlling particular diseases, such as smallpox or polio; in managing groups of linked health problems, such as diarrheal diseases; in managing the health problems of key subpopulations, such as mothers and children; or in structuring activities, such as immunization.<sup>1</sup> Attractive to international donors and partners, they are usually well-funded through extra-budgetary resources, tightly managed, with specific objectives and highly qualified personnel.<sup>2,3</sup> It has also been noted that vertical programs are most appropriate when the technology of disease control is very sophisticated, and very different from common tasks requiring specific skills.<sup>3</sup>

Although always present, vertical health programs have grown in prominence over the past few decades as international funding for the priority health programs of LMICs has increased. However, problems were identified with disease-specific approaches as early as the 1960s, when a WHO study group on “the Integration of Mass Campaigns against Specific Diseases into General Health Services” reviewed both vertical and integrated approaches to public healthcare, and concluded that integrated approaches were more sustainable, efficient, and convenient for users.<sup>4</sup> The vision of comprehensive PHC articulated within the Declaration of Alma Ata in 1978 was, in some respects, a response to verticalized health programing. However, this vision was seen by many as too ambitious, in particular given public sector spending constraints imposed in many developing countries from the 1980s onwards.<sup>5</sup> Instead, selected strategies or interventions were promoted and ‘selective PHC’ ensued,<sup>6</sup> leading to programs such as the Expanded Program on Immunization, and the development of packages of “essential services”.<sup>7</sup>

## INTEGRATION IN SRH

Within the field of SRH, similar tensions have evolved. A narrow focus on family planning programs and population control in many countries, to the neglect of broader SRH goals and women’s rights, led to the call for a comprehensive and integrated response to SRH care. At the International Conference on Population and Development (ICPD) in 1994, 179 countries signed up to a Programme of Action on delivering this comprehensive package of services, which included family planning; abortion (where legal) and management of abortion-related complications; antenatal care (ANC), delivery, postpartum, and newborn care; and the prevention and management of infertility and RTIs and STIs including HIV.<sup>8</sup> This pledge has been re-emphasized through various other international policy documents since then, including ICPD reviews in 1999, 2004, and 2009; and through WHO’s *Reproductive health strategy to accelerate progress towards the attainment of international development goals and targets*,<sup>9</sup> as well as through the renewed commitment to achieving universal access to reproductive health by 2015 as part of the Millennium Development Goals global strategies<sup>10</sup> (see Box 19.1 for a full list of policy statements on SRH integration).

Yet again, however, the reality of trying to deliver a comprehensive package of care in resource-constrained settings with weak PHC infrastructure inhibited fulfilment of these integration goals. In the late 1990s, evidence emerged of the difficulties confronting reproductive health services in expanding beyond their service focus and their traditional patient base of married women.<sup>11–13</sup> Many programs were failing to reach out to target groups with the greatest sexual health needs, namely men and adolescents. Programs also lacked the capacity to develop feasible, acceptable, effective, and cost-effective strategies, especially for delivering STI management.<sup>14,15</sup> Integration within SRH programs therefore became a compromise between the rhetoric of comprehensive care and the reality of service delivery.<sup>11</sup>

### Box 19.1 International Policy Documents on Integrated SRH Care

- Glion Call to Action on Family Planning and HIV/AIDS in Women and Children.<sup>96</sup>
- New York Call to Commitment: Linking HIV/AIDS and Sexual and Reproductive Health.<sup>32</sup>
- Reproductive health strategy to accelerate progress towards the attainment of international development goals and targets.<sup>9</sup>
- World Summit Outcome.<sup>10</sup>
- The global elimination of congenital syphilis: rationale and strategy for action.<sup>56</sup>
- Global strategy for the prevention and control of sexually transmitted infections: 2006–2015.<sup>57</sup>
- Sexual and reproductive health and HIV/AIDS: a framework for priority linkages.<sup>97</sup>
- Report of the International Conference on Population and Development.<sup>8</sup>
- Key actions for the further implementation of the Programme of Action of the ICPD+5.<sup>98</sup>
- UNGASS Political Declaration on HIV/AIDS (June 2006).<sup>99</sup>

## HIV PROGRAMS

At the same time as challenges to SRH integration were being identified, the HIV pandemic was emerging and substantially increasing international funding to HIV and other communicable diseases through mechanisms such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), and through initiatives such as the US President’s Emergency Fund for AIDS Relief (PEPFAR).

While family planning and MCH programs evolved either within, or closely connected to PHC programs, HIV programs, on the other hand, mostly evolved as specialist vertical programs from the outset. This specialization was fuelled by donors and technical specialists who were more focused on the epidemiological and clinical aspects of infectious disease control.<sup>16</sup> As the epidemic grew exponentially in the early 1990s, the rationale to focus on HIV separately from other health programs became even stronger. The creation of a separate United Nations agency on HIV in 1996 (UNAIDS) demonstrated clearly the impetus to tackle the virus within a specialized framework, independent of other SRH problems and other infectious diseases.<sup>17</sup>

Over the past 5 or 10 years, however, weaknesses of the health systems within which HIV programs were being implemented have prompted recognition of the need to address the disease through a more integrated approach. As a consequence of the strong financial support that HIV programs received, they have often been found to be stronger than the prevailing PHC structure within which they are operating. Studies even began to report on the integration of primary care services *into* vertical HIV services.<sup>18,19</sup> Not only has there been a shift to a “public health approach” to HIV management,<sup>20</sup> but also a multitude of calls to use HIV funding for health systems strengthening.<sup>21,22</sup> Evidence has also emerged that strengthening healthcare through the use of HIV funds can also benefit other health services, including reproductive health services.<sup>23</sup> Lastly, since HIV is a chronic condition that requires a wide range of interventions and activities along a continuum of prevention, diagnosis, treatment,



and palliative care, its placement under verticalized programs may not be cost-effective in the long term: in essence, any vertical HIV structure has no choice but to duplicate virtually a standard multi-function health service.<sup>1</sup> The long-term need for chronic care therefore provides a strong rationale argument for the management of HIV within an integrated structure.

## A FALSE DICHOTOMY

Given the potential of using vertically funded programs to strengthen health systems, the dichotomy between vertical and horizontal approaches may be a false one. Further, many interventions may be organized by vertical management structures but delivered through primary or integrated programs.<sup>3</sup> Within more developed health systems, it is clear that strong PHC can be supported by vertical structures and specialist medical programs. General practitioners (GPs) in the United Kingdom, for example, interact within multi-disciplinary teams and are supported by a highly specialized medical system at the secondary and tertiary levels. Various reviewers have concluded that optimal care must be based on a synergy of vertical and horizontal approaches, with specific models based on local epidemiology, organizational, functional and resource capacities, and the socio-cultural values of the country.<sup>1,3,5,16</sup> This has become manifest in the approach of hybrid 'diagonal' health financing which aims to utilize vertical funds to strengthen health systems.<sup>24</sup>

## Understanding Integration

While a considerable literature on integration of STI and other SRH services has been published in recent years, the concept often remains poorly defined. Integration in the health sector should be understood as both a process (the action of integrating) as well as an outcome in itself (integrated services). The former implies bringing together two or more components of care that were previously separate, or adding new components of care to an existing service, resulting in a range of organizational changes to service provision.<sup>25</sup> Integrating care in this way is used as a tool to overcome fragmented healthcare within systems where vertical disease-specific programs predominate. The concept of *integrated* care, on the other hand, is often equated with comprehensive PHC, and implies the delivery of a core package of services.<sup>1</sup> A 1990s WHO study group on integrated care defined integrated services as holistic, comprehensive PHC, organized through a decentralized and efficient district health system.<sup>5</sup>

Various typologies of integration have been proposed over recent years and they describe the concept at different levels of program management and delivery. It has been categorized as either 'functional', implying the integration of different healthcare functions,<sup>5,26,27</sup> or 'organizational' or 'administrative', implying the integration of management structures and processes, but not necessarily bringing together service tasks.<sup>26</sup> To some, while administrative integration may be helpful, functional integration is the important endpoint to provide holistic, integrated care to patients.<sup>26</sup> Integration has also been described as the 'bundling

of services', implying an integrated approach to client or patient management<sup>28</sup>; a useful example being the Integrated Management of Childhood Illnesses (IMCI). It can also be categorized as 'temporal', implying integration at one point in time so that a patient can access any type of care at each contact with the health service, or 'spatial', with all services provided by the same team or in the same room, but perhaps at different points in time.<sup>1</sup> This last also implies that integration is a 'continuum', implying continuity of care over the life-course.<sup>29</sup> Within the context of SRH, STI, and HIV, integration can also occur at the preventive level (information, education, and behavior change), the treatment level (clinical diagnosis and management), and at a policy level.<sup>30</sup>

When considering service delivery, it can be useful to classify different types of integration, including 'provider-level integration', meaning a range of component services are offered by one provider; or 'room-level integration', meaning a range of services are offered in one room (which may or may not be given by one provider); or as 'facility-level integration', with patients accessing different components of care within one site, but with different providers and in different rooms. While some may dispute this last as being integrated care, others consider it as such as long as the provider actively encourages patients to use other services during that visit.<sup>12</sup> Integration can also be considered as 'active', implying that providers must assess a range of possible health needs over and above a presenting problem or condition; or 'responsive', implying that patients are the ones who take the initiative to discuss their problems and demand a service response.<sup>31</sup>

At a more programmatic level, the terms 'linkages' or 'synergies' between more verticalized health programs have gained currency in recent years.<sup>32</sup> This is primarily borne out of the recognition that not all services can or should be delivered at one point in time by one provider, as well as the realization that subspecialist or specialist care will always be required at some level. What is important, therefore, is to build strong linkages between different programs and ensure that effective referral and continuity mechanisms are in place between different levels and different types of healthcare.<sup>33</sup>

Ultimately, therefore, integrated care implies either having multi-purpose staff, a multi-purpose team and clinic, or an effective referral mechanism to address a range of different healthcare needs.

## Rationale for Integrated Approaches in SRH

Unintended pregnancy and STIs, including HIV, often share the same root cause, namely unprotected sexual intercourse. Considering HIV specifically, the majority of infections in most settings are sexually transmitted or are associated with pregnancy, childbirth, and breast-feeding. In addition, the various SRH morbidities share root causes, including poverty, limited access to appropriate information, gender inequality, cultural norms, and social marginalization of the most vulnerable populations.



Many have therefore considered it logical for reproductive health services to be at the forefront of efforts to prevent STIs and the sexual transmission of HIV.<sup>14</sup> The presumed benefits of integrated approaches will be discussed.

## PATIENT SATISFACTION

Provision of a relatively broad range of services within one clinic or by means of a single visit to one provider has been assumed to increase patient satisfaction with care. In verticalized or disintegrated services, patients may have to visit several facilities to address diverse SRH needs, or may have to queue multiple times within one facility. In fee-paying institutions, patients may also achieve savings in settings where they can get all their services in one visit. However, while having all your health needs addressed within one visit may have clear advantages for the consumer, the integration of STIs and HIV into reproductive health consultations may also have its drawbacks for some patients. It may require that a risk assessment of sexual behavior be conducted, and in some instances a pelvic examination as well, both of which may be off-putting. Older, married women may take offence at the suggestion that they may be at risk for STIs. Further, patients who are in a rush, for example repeat ART users coming for monthly refills, or repeat family planning patients coming for injections, may object to STI screening, or other SRH counseling if initiated by the provider.

## SERVICE ACCESS AND COVERAGE

Integration has been proposed as an important means to increasing health equity by increasing access to and utilization of services. In many settings where transport is costly and unreliable, where queues are long and patient loads are high, providing a range of services through one provider or under one roof (i.e., a 'one-stop-shop') should theoretically increase access to and use of services. In many settings, referral systems between different health institutions are weak, and patients referred either internally or externally may not reach their destination. One study from West Bengal, for example, found that adding HIV testing and counseling within a functioning SRH service (as opposed to referring patients to a separate service adjacent to it) led to uptake of both SRH and HIV service arms, as well as reducing costs.<sup>34</sup> An integrated service may also expand the patient-base of services. Specifically, integrated approaches can help reproductive health programs move beyond their focus on women, and involve men, adolescents, sex workers, and other high-risk groups within a more comprehensive healthcare program.

However, referral models may also be effective in certain circumstances. One African study that compared a referral model of HIV testing within a family planning service with an on-site model found mixed results: although providers at the on-site model were more effective at offering HIV testing to family planning patients, those attending the referral model were more likely to accept a test.<sup>35</sup> The authors suggested that this difference reflected a preference for anonymous testing at

a separate site. Further, even in purportedly integrated settings where providers have been trained to deliver a broader package of care, missed opportunities for integrating care persist. In particular, what is unclear is how providers of integrated services manage to move beyond the condition presented by the patient to explore other health topics, i.e., the process of "active integration" discussed earlier. One report shows that breadth of service can be increased through the use of screening algorithms, although it also indicates that a high patient-load can be prohibitive to increasing the number of services accessed per visit, even when providers are supported by training and job aids.<sup>47</sup> The provider role is particularly important for STI services, given that patients in many contexts rarely take the opportunity to report STI/RTI symptoms spontaneously in consultations.<sup>36</sup> Furthermore, studies conducted in integrated health centers have shown that patients are also often unaware of the range of services available to them.<sup>37</sup>

## STIGMA, PRIVACY, AND CONFIDENTIALITY

During the 1990s, there were concerns that addressing STIs within reproductive health contexts would be stigmatizing for those patients attending for STI services, and that providers of family healthcare would have difficulty in adjusting to meet the needs of a high-risk group.<sup>16</sup> On the other hand, offering STI and HIV services through services not identifiable with first-line STI or HIV care may reduce the risk of social stigma for patients and reduce barriers to services such as HIV testing or STI management.<sup>32,38</sup> A review of program effectiveness of the integration of STI and HIV with family planning services found no evidence that integrated services increased stigma toward services or patients, and may indeed be a more comfortable environment for patients.<sup>39</sup> However, the value of integrated care in reducing service-related stigma is dependent on the degree to which reproductive health services are able to maintain confidentiality. This may be jeopardized where STI or HIV patients are seen in consultation rooms clearly marked for their care. Moreover, some evidence suggests that people living with HIV may prefer specialized HIV care to integrated care because of the poor treatment they receive in integrated services, including lack of confidentiality and privacy, discrimination and negative attitudes from providers, and otherwise substandard care.<sup>40,41</sup>

## QUALITY OF CARE

Integrating a new service component into an existing service has the potential to improve quality of care by increasing the breadth of care and by providing more patient-centered care, or to diminish quality as breadth is achieved at the expense of depth.<sup>42</sup> In particular, quality may suffer as providers struggle to broaden their scope of care to more sensitive areas of sexual health counseling and care. Although in theory reproductive healthcare providers already possess many of the technical and service skills required to offer STI-related information and services for prevention, studies suggest providers of reproductive healthcare face difficulties in

addressing STI and HIV prevention and conducting behavioral risk assessments for patients.<sup>43–45</sup> Many studies published in the late 1990s also found that reproductive healthcare providers were struggling to effectively deliver quality STI services as programs lacked the capacity to develop feasible, acceptable, effective, and cost-effective strategies for STI management.<sup>14,15</sup> These challenges are discussed further under heading “Challenges and Strategies for Integration”.

### COST-EFFECTIVENESS

Integration of services can improve efficiency through the optimal use of scarce resources and avoiding duplication of effort. It offers cost savings by sharing staff, facilities, equipment, and other administrative and overhead costs.<sup>14,16</sup> Cost-savings seem most likely when many patients are able to access more than one service, as has been demonstrated in a recent Indian study integrating SRH and HIV services.<sup>34</sup> In another Kenyan example, the combined costs of integrated HIV and family planning services amounted to less than half the estimated costs of a stand-alone VCT site.<sup>35</sup> However, it seems clear that staff must have excess time available before service integration begins if cost-effectiveness or increased productivity is to be achieved.<sup>46,47</sup>

### IMPACT ON HEALTH

Investigating a direct link between a service delivery configuration and health outcomes is problematic, given the diverse range of other determinants on health outcomes. In theory, making improvements in the areas already discussed, such as access, coverage, and stigma, should ultimately lead to improved outcomes. Lower level outcomes may be more realistic to measure and achieve, for example improved condom utilization where STI and HIV prevention interventions have been added to a family planning service; higher rates of HIV testing and access to HIV care and treatment following integration; or higher rates of STI screening and treatment in integrated settings. For example, two recent pre- and post-test studies on integration of HIV testing into FP services in South Africa and Kenya reported significant increases in discussions of condom use and dual-protection counseling.<sup>35,48</sup> Another report from Ethiopia found that being attended by the same provider in the same room was positively associated with patient-initiated HIV testing and negatively associated with patients' HIV infection, compared with being seen elsewhere in the facility.<sup>49</sup> Important, *albeit* limited, evidence is also emerging that promotion of FP for HIV-infected women (usually as part of FP/MCH services) can reduce pediatric HIV by preventing unintended pregnancies, a strategy likely to be significantly more cost-effective than the provision of PMTCT.<sup>50</sup>

### Models of STI Integration

STI services are most commonly delivered within the context of PHC, SRH care, or more specialized STI and HIV services. A range of different health services make up the different

components of SRH and HIV care, and within these feature a range of possible interventions that can be delivered to broaden the service scope of a pre-existing (or ‘baseline’) service. Table 19.1 gives an overview of the different service configurations that are possible for integration. These services and interventions will be discussed in this section, with a focus on scaling-up access to STI prevention, care, and treatment.

Before discussing the details of service configurations, however, it is worth noting that the exact model of integration within a health system is dependent on the context in which it is being undertaken. Integration is shaped by the mission of the organization involved, the local context, the needs of the patients and the community, the potential local partnerships for referral, and the organization's own capacity.<sup>51</sup> It is also influenced by the epidemiological context, in particular the STI and HIV prevalence and distribution. It is therefore critical to assess the current health systems and service structures and review current service configurations and identify gaps in service delivery.

### SERVICES AND INTERVENTIONS INTEGRATING STI AND HIV INTO SRH SERVICES

Integration of STIs and HIV into other reproductive health services include four main groups of activities: firstly, primary STI and HIV prevention (including health education and counseling, and provision of educational materials and condoms); secondly, the diagnosis and management of STIs, (screening, diagnosis, clinical management, treatment or referral for treatment, partner notification, and secondary preventive counseling); thirdly, integration of HIV services into SRH, including PMTCT, HIV testing, and treatment; and lastly, integration of other SRH services.

### STI and HIV Prevention

On the prevention side, reproductive health services can be used to promote safe sex. In its guidelines on both family planning and STI integration, WHO recommends that counseling on STIs become an integral component of contraceptive decision-making and maternal health counseling.<sup>52,53</sup> Family planning patients should be counseled on the effectiveness of contraceptive methods for infection prevention, as well as contraceptive efficacy. Different protection strategies can be suggested to patients, including dual protection (condoms alone or with another method), safer sexual practices, delayed sexual debut, and partner reduction (where relevant).

However, the promotion of condoms in reproductive health programs presents a challenge. Over the past 30 years, providers have generally favored more technically advanced, effective, and longer-term methods, disregarding the condom as an effective method for preventing unintended pregnancy. Condoms, where promoted, have almost exclusively been targeted at young people, with an emphasis on use for nonmarital sexual contacts. Efforts are needed to change the beliefs and practices of providers, to promote the emphasis on both prevention of pregnancy and

**Table 19.1:** SRH and HIV Integrated Services and Strategies\*

Existing SRH services			Existing STI and HIV services		
Baseline service plus	Services	Selected key interventions	Baseline service plus...	Services	Selected key interventions
Family planning +	<ul style="list-style-type: none"> <li>STI management</li> <li>HIV testing</li> <li>Condoms</li> <li>STI and HIV prevention counseling</li> <li>Cervical cancer prevention</li> <li>Infertility</li> <li>Breast cancer screening</li> <li>Violence services</li> </ul>	<ul style="list-style-type: none"> <li>Routine pelvic examinations</li> <li>Syndromic management of STIs</li> <li>Pap smears or VIA</li> <li>VCT or PITC</li> <li>Screening for violence</li> </ul>	STI +	<ul style="list-style-type: none"> <li>Family planning</li> <li>Condom provision</li> <li>HIV testing</li> <li>Prevention counseling</li> <li>Violence services</li> </ul>	<ul style="list-style-type: none"> <li>Condom promotion</li> <li>VCT or PITC</li> <li>Screening for violence</li> </ul>
ANC +	<ul style="list-style-type: none"> <li>STI management</li> <li>HIV testing</li> <li>PMTCT</li> <li>Family planning counseling</li> <li>Violence services</li> </ul>	<ul style="list-style-type: none"> <li>Syphilis screening</li> <li>Other RTI/STI screening</li> <li>VCT or PITC</li> <li>Screening for violence</li> </ul>	VCT +	<ul style="list-style-type: none"> <li>Family planning</li> <li>Condom provision</li> <li>STI management</li> <li>Prevention counseling</li> </ul>	<ul style="list-style-type: none"> <li>Condom promotion</li> <li>Syndromic management</li> <li>Presumptive STI treatment</li> <li>Referral to ART</li> </ul>
Delivery care +	<ul style="list-style-type: none"> <li>PMTCT</li> <li>STI management</li> <li>HIV testing</li> </ul>	<ul style="list-style-type: none"> <li>ART prophylaxis</li> <li>Breastfeeding counseling</li> <li>VCT or PITC</li> </ul>	PMTCT +	<ul style="list-style-type: none"> <li>Family planning</li> <li>Pregnancy planning</li> <li>Condoms</li> <li>STI management</li> <li>Prevention counseling</li> <li>ART</li> </ul>	<ul style="list-style-type: none"> <li>Condom promotion</li> <li>Syndromic STI management</li> <li>Referral to ART</li> </ul>
Postpartum care +	<ul style="list-style-type: none"> <li>HIV testing</li> <li>ART</li> <li>Prevention counseling</li> <li>Family planning</li> <li>Pregnancy planning</li> <li>STI management</li> </ul>	<ul style="list-style-type: none"> <li>(Repeat) HIV testing for mother</li> <li>Neonatal HIV testing</li> <li>Repeat infection screening, including screening for neonatal syphilis</li> </ul>	HIV care and treatment +	<ul style="list-style-type: none"> <li>Family planning</li> <li>Pregnancy planning</li> <li>Sexual health</li> <li>Condom provision</li> <li>Cervical cancer</li> <li>STI management</li> </ul>	<ul style="list-style-type: none"> <li>Positive prevention counseling</li> <li>Assisted reproduction (counseling or treatment)</li> <li>Sexuality counseling</li> <li>Pap smears</li> <li>Syndromic STI management</li> <li>Routine gynecological exams</li> </ul>
Post-abortion care/ abortion care +	<ul style="list-style-type: none"> <li>HIV testing</li> <li>Prevention counseling</li> <li>Family planning</li> <li>Pregnancy planning</li> <li>STI management</li> <li>Violence services</li> </ul>	<ul style="list-style-type: none"> <li>VCT or PITC</li> <li>Condom promotion</li> <li>Syndromic STI management</li> <li>Infection control</li> <li>Screening for violence</li> </ul>			

\*Table adapted from Askew.<sup>32</sup>

PITC, provider initiated testing and counseling; PMTCT, prevention of mother-to-child transmission; VCT, voluntary counselling and testing.

protection against infection. Research has also shown that the promotion of condom use within marriage is achievable.<sup>54</sup>

Delivering more holistic sexuality counseling can also be an important preventive intervention. Discussing sexual behavior helps patients understand better their own risk of both unintended pregnancy and STI and HIV infection.<sup>28</sup> Studies have shown that many patients have concerns about their sexual health and appreciate the opportunity to ask questions and share their problems in a safe environment.<sup>55</sup> However, health workers need to be properly trained to introduce discussions around sexuality into reproductive health services.

## STI Screening, Diagnosis, and Management

Integrating the detection and management of STIs and RTIs into some reproductive health settings can be more complex, and is limited to a large degree by current technologies and resources available. Screening for STIs may be undertaken in well-resourced centers, including speculum and bimanual examination to look for signs of cervical infection or PID, screening for early diagnosis of cervical cancer, or screening tests for syphilis, chlamydia, or gonorrhea. Most tests available are complex and costly, require intensive training for providers and are simply not feasible in



resource constrained settings.<sup>56</sup> Furthermore, the current costs of providing laboratory screening for many STIs is beyond the resource capacity of most public health systems in many LMICs. In one African country, for example, the estimated additional cost of laboratory screening per family planning visit would be over US\$25.<sup>14</sup>

The recent development of point-of-care diagnostic tests (rapid tests) is a major technological development that can support integration of STI services into reproductive healthcare.<sup>57</sup> Until recently, syphilis screening was limited to pregnant women, but access can now be scaled-up through the use of rapid tests which can be performed outside a laboratory setting with minimal training and no equipment. Research is also currently being conducted on the development of rapid tests for chlamydia and gonorrhea.<sup>58</sup> Nevertheless, given the scarcity of STI diagnostic tests, syndromic management remains the core intervention in the WHO strategy for STI control in resource-poor settings, delivering immediate prevention and care for people presenting with clinical syndromes usually associated with the presence of an STI or RTI.<sup>57,59</sup> The value of the syndromic approach is that it is relatively simple to use, and can be incorporated into all levels of the healthcare system, in both the public and private sectors. It was through this approach that most reproductive health services began to integrate STI treatment into their services in the 1990s. However, its poor performance in managing abnormal vaginal discharge in women means that is not a magic bullet for STI control within primary care settings, and WHO now recommends that the management of vaginal discharge should be based on the assumption that the infection is a vaginal infection.<sup>53</sup>

A range of STI screening interventions are also recommended during and after pregnancy and in childbirth. These include STI and RTI assessments in ANC; provision of syphilis screening, treatment, and partner treatment; testing for bacterial vaginosis and trichomoniasis if there is a history of spontaneous abortion or preterm delivery; an offer of VCT and access to PMTCT for positive women.<sup>53</sup> During labor and delivery, actions should also be taken to identify infections that may not have been detected during ANC, and to intervene where possible to prevent and manage STIs and RTIs in the newborn.

## HIV Services

Different strategies to scale-up HIV within PHC and SRH testing include VCT (allowing patients to independently make a choice to attend a health facility to get an HIV test), and more recently, provider-initiated testing and counseling (PITC) (encouraging the promotion of HIV testing within a range of different health settings through an “opt-out” approach).<sup>60</sup> In all HIV epidemics (whether low-level, concentrated or generalized), WHO now recommends that HIV testing should be proposed by healthcare providers as part of standard care to all clients or patients who present with signs or symptoms that could indicate HIV infection; to infants born to HIV-positive women; to malnourished children who do not respond to nutritional therapy;

and to men seeking male circumcision. Within generalized epidemics (where prevalence is consistently over 1% in pregnant women), WHO recommends that HIV testing be recommended to all adults and adolescents seen in health facilities, including all those attending any kind of SRH service.

PMTCT services are another critical HIV service that may need to be integrated into reproductive healthcare. Such programs usually consist of upgrading basic MCH services to include the introduction of HIV testing, ARV prophylaxis for HIV-infected pregnant women, safe delivery practices, counseling and support for safe infant feeding practices, follow-up of HIV-positive women, and prevention counseling with condom promotion.<sup>61</sup> In addition to these core services, however, other elements of SRH care for positive women may need to be considered (see next section). Follow-up of HIV-positive mothers is also a critical issue for an integrated service. In many programs in LMICs, women do not continue to receive ART outside the PMTCT program. Care is usually limited to referral to community-based care and support services. However, fear of stigmatization may make women reluctant to disclose their HIV status either in or outside the ANC clinic.

## Other Interventions

Other services and interventions that can be provided within an integrated SRH service include infertility counseling and treatment, cervical cancer screening and treatment, and violence services.

Most of the infertility in LMICs is attributable to damage caused by RTIs or STIs, notably gonorrhea and chlamydial infection, making it an important SRH concern that services must address. Aside from primary prevention and treatment of infections, other possible strategies include addressing unsafe abortion and substandard obstetric care, providing infertility treatments through assisted reproductive technologies and providing comprehensive counseling for infertile couples. One successful program was implemented by the Family Planning Association of India (see Box 19.2).

Cervical cancer prevention, screening, and treatment are also important services that may be integrated into pre-existing primary care settings. Primary prevention through the HPV vaccine is an ideal way to prevent infection, since most people are exposed once they become sexually active. However, since the target cohort for the vaccine is girls aged 10 to 13 years, SRH services may not play a large role in national roll-outs. On the other hand, reproductive health services, in particular family planning programs, offer an important opportunity for screening. Screening and treatment programs have been shown to be effective in reducing mortality in women since the cure rate for invasive cervical cancer is closely related to the stage of disease at diagnosis and the availability of treatment. However, achieving a high level of coverage is essential for cancer control programs, and organized national prevention programs are most cost-effective.<sup>62</sup> Since Pap smears are generally used for screening only in middle- or high-income settings, one low-cost option that can be integrated into SRH is visual inspection with acetic acid (VIA).<sup>63</sup> The



**Box 19.2** Program Examples Integrating STI/HIV and Other Healthcare into SRH Services***Integrating STI into reproductive health services in sub-Saharan Africa and Indonesia***

In pilot projects conducted in Kenya and Zimbabwe, family planning and ANC services were systematically reoriented to include STI control and treatment. Following a needs assessment, staff were trained, drug supplies guaranteed, and a standardized checklist developed to guide staff through all components of an integrated consultation. This consultation comprised a full history, a clinical examination (including pelvic examination), a risk-assessment, and education on STIs and HIV. Research found the various reorientation activities were important, and that use of the counseling checklist, in particular, was useful to guide providers through an integrated consultation.<sup>13,101</sup>

Experience from Indonesia has shown that integration of STI prevention and care into family planning clinics is feasible even in low prevalence settings, and does not necessarily require large infrastructural investments. A pilot program in North Jakarta demonstrated that the equipment and supplies available at the community health center were adequate for the provision of integrated services. It was found that being able to offer privacy and confidentiality in a well-run clinic, coupled with well-trained providers with nonjudgemental attitudes, were key to success. An important lesson was that the process of reorienting and training providers to integrate STI prevention and care into family planning settings took more time than expected.<sup>102</sup>

***Adding HIV services to SRH in India***

The Family Planning Association of India integrated HIV services into SRH care in Lucknow. The needs and feasibility assessment was conducted first. Staff were initially sceptical about adding VCT to their workload, since they felt that it might change the profile of service users, that the patient perception of the clinic might change, and that the HIV services might take over the clinic. There were also concerns about increased staff workload, as well as occupational exposure to HIV. In this situation, integration of services was achieved gradually: nurses began to explore their patients' risk of STIs and HIV, so they could refer them to VCT services. Educational materials were developed on HIV prevention and care, and activities were carried out to raise awareness of HIV in the clinic. Procedures for universal precautions and sterilization of equipment were also reviewed and revised to reduce fears about occupational exposure. After several months, all staff saw that they had an important role in HIV services, and in maintaining a low rate of HIV prevalence in the region, and full integration of services could commence.<sup>51</sup>

***Infertility care within SRH***

The Family Planning Association of India incorporated infertility care into its *Comprehensive Reproductive Health for All* project. One of the first areas to roll out this service was Bhiwandi, where a specialized infertility service was integrated with other reproductive health services.<sup>102</sup> The program included staff training and the development of new standards and protocols for infertility care. A specialized infertility clinic was organized at certain times of the week, where couples (rather than individuals) could be counseled. Infertility services provided included screening and diagnosis of infertility (including semen analysis for men, and physical examinations, cervical mucus studies and blood tests for women), diagnosis and treatment of STIs, counseling and education on fertility and the menstrual cycle and provision of counseling and emotional support for couples with primary infertility. Treatments for infertility included counseling on effective sexual intercourse practice (extending intervals between ejaculations to allow sperm counts to build up), sperm washing, artificial insemination, and referrals for more sophisticated treatments (such as testicular sperm aspiration and sperm auto-preservation). Infertility services proved to be one of the more popular services offered at the clinics, forming one-tenth of the total patient load. However, despite these advances, this clinic was also limited by the local health system capacity. Staff were not able to diagnose the cause of infertility in the majority of cases (65%) due to the high costs of diagnostic techniques and the difficulties of infertility diagnosis. Also, many of the treatments offered were costly, and would be beyond the reach of the poorest patients.

***Addressing violence within SRH in Brazil***

Both government and NGOs are responding to violence against women in Brazil. In government facilities, services were created in a number of hospitals to address the consequences of sexual violence. The programs offered emergency contraception, prophylactic antibiotics for syphilis, gonorrhea and chlamydial infections, immunization against hepatitis B, antiretroviral drugs to prevent HIV transmission, pregnancy termination, and psychological counseling. Women were also advised to report assaults to the police. On the basis of these experiences, the Ministry of Health in 1998 published standards for the prevention and treatment of the consequences of rape in adult and adolescent women. The number of hospitals offering such services increased from 3 in 1997 to 71 by the end of 2001.<sup>104</sup>

The Brazilian Civil Society for Family and Well-being (BEMFAM) started including services for victims of gender-based violence in its SRH services in 2000. The first phase concentrated on improving the knowledge and attitudes of health staff. In several workshops, methods of sensitizing staff to the problem of gender-based violence were tested, and a service protocol was developed. Systematic screening was started in 6 clinics to collect data on the prevalence of gender-based violence, and its different types. The need for a referral network soon became apparent, since health workers were reluctant to screen if they could not offer services. BEMFAM has compiled a directory of existing services for victims of gender-based violence.<sup>105</sup>

development of effective follow-up and referral mechanisms is also an integral component of screening programs.

SRH services may also offer a potential entry point for identifying and addressing violence against women (VAW).<sup>64</sup> Health services should be prepared and health providers trained to respond appropriately to VAW and, where appropriate, to recognize signs of intimate partner violence and other forms of sexual violence. Strategies include screening, treatment, and referrals to more specialized care. There is, as yet, no consensus on whether, when and how women should be systematically screened, in particular for intimate partner violence, since screening may impact on a woman's future risk of violence. Screening processes must ensure privacy and confidentiality, and be conducted in

safe and nonjudgemental ways. Within SRH, the provision of post-rape services is critical, including providing emergency contraception, abortion services, post-exposure prophylaxis (PEP) for HIV and other STIs, counseling and referral to other medical, psychological, social, and legal services. Violence services can also be provided through separate specialized facilities, for example through "One-Stop Crisis Centres", which are often co-located with emergency departments in hospitals.<sup>65</sup>

**INTEGRATION INTO STI AND HIV SERVICES**

Although most emphasis continues to be placed on integration of STI and HIV services into reproductive healthcare and other

primary care settings, some programs have also begun to integrate family planning or other SRH care into newly emerging STI and HIV services. This section will discuss strategies for both integration into specific STI services, and also integration aimed at meeting the SRH needs of people living with HIV (PLHIV).

## Integration into STI Services

More specialized STI services may need to consider addressing the broader SRH or HIV needs of their patients. Such services may be targeting high-risk groups, such as sex workers or men, who also have other healthcare needs beyond STI treatment. Many STI services also continue to have too narrow a focus on treatment, neglecting an important opportunity for prevention counseling and condom promotion with patients who are evidently at high-risk. Box 19.3 contains an example of an Indian STI program that was successful in moving beyond its narrow focus to deliver more holistic care, including family planning and HIV services. STI clinics also play an important role in identifying PLHIV and in managing their STIs.<sup>66</sup>

## Integration into HIV Services

HIV services, including both VCT and treatment programs, need to consider a broader and more integrated approach to meet the diverse needs of their patients.<sup>67</sup> Studies have shown that a high percentage of VCT and PMTCT patients have an unmet need for family planning services.<sup>19</sup> Many programs are now using VCT as an entry point to deliver family planning and other SRH services (see Box 19.3). If patients test HIV-positive, they may have multiple health needs. Not only are PLHIV vulnerable to SRH problems, such as STIs, but they are also often in need of counseling on reproductive choices. Advances in ART provide renewed optimism about the future and increased confidence in having children. Studies have shown that PLHIV in many settings have unmet needs for contraception, as well as for counseling on pregnancy planning, abortion, infertility, and sexuality, among others.<sup>68–70</sup>

Many health professionals perceive the SRH needs of women living with HIV to be almost exclusively related to PMTCT, which has led to insufficient attention being paid to their other reproductive needs.<sup>71</sup> HIV-positive women face a range of dilemmas, discrimination, and barriers in upholding their reproductive rights to pregnancy and motherhood. Sexuality counseling has seldom been part of the counseling for positive women, since programs have tended to focus on the negative aspects of HIV, and have shied away from promoting positive living.<sup>72</sup> Women and men living with HIV report fear of infecting others, fear of disclosure, and violence and discrimination if their HIV status becomes known. They also report guilt, shame, anger, and ill-health resulting in physical and psychological effects on sexual desire and pleasure. In addition, the widespread promotion of abstinence by religious and public health organizations has contributed to the expectation that people with HIV should no longer have sexual lives.<sup>73</sup> Furthermore, HIV-positive women may experience a negative impact on their sexuality from HIV disease itself or from the side-effects of ARV drugs.<sup>74</sup>

### Box 19.3 Program Examples Integrating SRH into STI/HIV Services

#### *Integrated SRH services for sex workers in Mumbai, India*

The Aastha Project, run by FHI, is a community-led initiative in Mumbai that provides preventive and clinical services to sex workers, coupled with the promotion of an enabling environment through social mobilization and empowerment initiatives. Within the service component, STI clinics acted as hubs for the provision of family planning and HIV services to sex workers. The comprehensive package of services offered included screening and testing for STIs, counseling on safer sex and condom use, treatment compliance, partner treatment and risk reduction, advice on family planning, and referrals for additional services. The delivery of services at static clinics was supplemented by outreach visits to sex worker residences and work areas, as well as satellite clinics and mobile clinics to deliver services to hard-to-reach populations. Family planning services were integrated after sex workers expressed a need for reproductive healthcare: many had regular partners and required long-term effective contraceptive methods in addition to condoms. To achieve integration, existing protocols were modified, health providers were trained, the clinics' service delivery system was upgraded and expanded, a strong referral network was built, and community outreach activities were conducted.<sup>106</sup>

#### *Addressing SRH at VCT in Haiti*

In Haiti, PHC services have been successfully integrated into stand-alone VCT services since 1985. The centers, run by the Groupe Haitien d'Etude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO), offered diagnosis and treatment of STIs, diagnosis and treatment of tuberculosis, family planning services, ART, and MCH programs, including PMTCT. The model was rolled out to 22 public and private health centers.<sup>107</sup>

#### *Addressing the SRH needs of PLHIV in Uganda*

In Uganda, The AIDS Support Organization (TASO) began providing ART services in the town of Mbale in 2004. Although TASO offered limited family planning services to HIV patients, it lacked a comprehensive family planning program. An integration initiative was then conducted in 2006, supported by the ACQUIRE Project, to deliver more comprehensive family planning services to PLHIV. Methods delivered were condoms, oral contraceptives, injectables, and emergency contraception, with a strong referral system for longer-acting methods. Integration activities included strengthening supervision, logistics, referrals, and training; the development of a training curriculum and provider job aid on the contraceptive needs of PLHIV; supervisory checklists; improved data collection systems; the integration of family planning messages into health education materials; the orientation of HIV community workers to family planning; and the development of radio spots on family planning for dissemination in the community. In addition, advocacy was conducted with TASO managers to allow family planning activities to be conducted. Operations research found, however, several challenges to integration, including the need for further training on family planning and on dual protection; problematic referral processes; stock-outs of contraceptives; problems with record-keeping; and limited services being offered to men.<sup>108</sup>

PLHIV who desire children may also risk infection or reinfection from a partner. In developed countries, this may be prevented by using artificial reproduction techniques such as sperm washing or artificial insemination techniques. In low-resource contexts, support can include advice on conception at the fertile time of the menstrual cycle, adoption, or simple techniques to introduce sperm into the vagina using a syringe for cases where the man is HIV-negative. In cases where the male partner is HIV-infected but the woman is negative, the

situation is more complex since there is no risk-free method to ensure safe conception. Ways to help reduce risk of transmission, include attempting conception while the male partner is on ART and viral load has been reduced to undetectable levels; timing conception at the fertile time of the menstrual cycle; and using PEP for the woman.<sup>61</sup>

## Challenges and Strategies for Integration

Many programs have identified challenges when trying to deliver integrated services. They will be discussed here along with proposed strategies to achieving successful integration.

### HEALTH SECTOR COORDINATION

Health sector coordination can represent a substantial hurdle to restructuring existing service organization or integrating new service components. Administratively, the different programmatic components of SRH may come under the control of different government departments or ministries, and these separate programs and institutions may have developed their own policies, drug lists, training manuals, and technical guidelines, with little interdepartmental consultation.<sup>75,76</sup> Persistent conceptual divisions exist between SRH and STI or HIV programs, and the implementation of separate policy strategies or frameworks inhibits the delivery of linked or integrated services on the ground.<sup>30</sup> Various strategies exist to overcome these difficulties, including merging overlapping ministries, the use of cross-departmental working groups or task forces, funding cross-departmental positions, or stipulating the use of donor disease-specific funds for integrated service use.<sup>75,77,78</sup> Integration may also be supported by health sector reforms, which aim to improve service organization by reducing programmatic duplication and merging vertical programs to enhance effectiveness.<sup>79</sup>

### ORGANIZATION AND MANAGEMENT ISSUES

Health program managers at district and local levels often have to deal with the consequences of poor coordination at the national or state level, and may be squeezed between conflicting vertical and horizontal strategies.<sup>1</sup> Local managers often receive few additional resources to fund changes in service structure and little guidance on change management. Service integration can also lead to the blurring of lines of accountability.<sup>77</sup>

Furthermore, integration requires organizational change. When considering integration of STI and HIV services into PHC or SRH services, existing structures may need modification to ensure privacy for consultations, which is particularly important for the provision of sexuality counseling, STI prevention and care, adolescent healthcare, and VAW services.<sup>65,80</sup> The integration of STI prevention and care services can be undermined by a lack of resources including examination equipment, drugs and supplies, and laboratory equipment.<sup>13,16</sup> Integrated commodity supply chains can be effective, for example through joint contraceptive and condom procurement,<sup>81</sup> but may also disrupt the delivery of

effective vertical services if the efforts are not carefully planned and coordinated.<sup>82</sup>

When considering adapting current services to reach out to a broader patient base for sexual health services, the configuration of existing services may need to be considered. Delivering care to those who may be uncomfortable attending ‘women-focused’ reproductive health units (e.g., men, young people, or sex workers) may require constructing semi-specialized units or facilities to cater to their specific needs.<sup>80,83,84</sup>

A lack of effective referral systems may prevent another obstacle to delivering comprehensive SRH services. PHC services are often unable to respond to the wide range of psycho-social and clinical SRH needs of their patients, and access to specialized services is critical.<sup>85</sup> Such systems require staff to know where and how to refer patients; functioning transport systems; communications between different units and levels of healthcare; and the development of integrated information systems across the health system, for example through the use of electronic records and documentation of referral agencies.<sup>29</sup>

Another factor for consideration is how to cope with the increasing demand for counseling. Integrated, individualized SRH counseling can place heavy demands on staff time. Studies have demonstrated, however, that additional time can be made available through more efficient ways of working (e.g., task shifting) or through more structured counseling sessions which tailor the provision of information to the patient’s needs and situation.<sup>46,86</sup> Group counseling is also popular and can be used to provide information to patients before an individualized counseling session. Time invested in preventive counseling must also be balanced against significantly greater treatment costs.

### HUMAN RESOURCES AND TRAINING

Reviews of SRH integration have identified staff-related factors as important barriers to integrated service provision, including: insufficient training and motivation (linked to poor supervision and management), heavy workload and burnout, lack of incentives or compensation for increased work load, staff frustration, medical hierarchies, fear of redundancy, and territorialism among specialist staff.<sup>39,78,87</sup> Resistance to integration can be particularly strong in settings with low HIV or STI prevalence rates, where the need for integration is not understood by those working at service level.<sup>30</sup> However, in some settings, clinics may be operating below full capacity, and there may be windows of opportunity to improve efficiency and extend service coverage using existing human resources. Task-shifting is a strategy now being employed in resource-poor settings, in particular to expand human resource capacity to scale-up access to HIV care and treatment.<sup>88</sup> Initial fears over increased workloads following integration may also be allayed as providers adapt to offering additional sexual health services and appreciate the benefits of meeting patients’ needs or enhancing their own skills.<sup>31,89</sup>

At another level, healthcare providers often find it difficult to discuss sexual health and behavior, or do not appreciate the



level of confidentiality required to address sexual health issues, especially for marginalized populations. Training methodologies are required that empower providers to assess the comprehensive healthcare needs of individual patients factoring in issues such as gender, interpersonal relations, and sexuality. Providers may also need to clarify—and possibly change—their own values and attitudes. Various training courses have been developed in recent years to support programs that integrate sexuality counseling into reproductive health services.<sup>90–92</sup> Where pilot and demonstration training models have proved successful, it will be necessary to update and revise medical and nursing school curricula to ensure that preservice training incorporates new subjects and new approaches, in addition to reinforcing in-service updates.

Training also needs to support a shift from a one-way provision of information to patient-centered counseling which can support more holistic diagnosis and care.<sup>93,94</sup> In many settings, healthcare is structured around the delivery of routine tasks and care is fragmented among teams of providers.<sup>95</sup> For example, care is often focused on procedures such as weighing, taking blood tests, completing standardized history forms, or drug prescribing. Providers thus consistently miss opportunities to integrate clinical care with other services, and the wider health and social needs of patients may be neglected.

One program in the UK attempted to integrate the subspecialties of family planning and genito-urinary medicine (GUM).<sup>42,94</sup> Two possible models of integrated training were identified: (i) comprehensive dual training, leading to a “new breed of consultants”; and (ii) a modular approach—to enable those working in one speciality to provide care in the other. The former was favored by advocates of integrated services since it was felt a modular approach would result in a two-tier system, with two groups of physicians working in parallel. However, specialists felt that dual training may not equip practitioners to deal with more complicated aspects of patient care. At another level, providers also felt that a more fundamental problem was the difference in structure and culture of the specialties of family planning and GUM. Practitioners saw family planning medicine as preventive and STI medicine as generally curative; family planning was seen as community-based while GUM was hospital-based; STI counseling was seen as directly focused on treatment of disease, while family planning counseling was seen as more interactive and empathetic. Clearly these kind of differences need to be resolved before integration can be attempted.

Providers also require support from their supervisors, not only at the outset of the program but throughout the process of change.<sup>28</sup> Without such support, health workers will be unable to do their work well, and their motivation and quality of work will suffer. There is a risk, however, that as services become integrated supervisors can lose their specialized competencies, which the service providers depend upon; so careful monitoring of training and supervision needs is required.<sup>77</sup>

## PATIENT MANAGEMENT AND COUNSELING TOOLS

Vertical patient management systems can prevent effective integration. For example, separate patient registers or patient record cards for the different components of SRH care may make it impossible for one provider to cover multiple areas. Integrating data monitoring and systems tools can therefore support service integration. Another way to support integrated counseling is the provision of screening tools and job aids, such as checklists or flipcharts, which can be used during counseling, to ensure that all relevant topics are discussed. Health workers may find it easier to start talking about sensitive topics when patients are aware that there is a standard list, which makes the questions seem more routine. WHO's *Decision-making Tool for Family Planning Clients and Providers*, a contraceptive counseling tool that includes STI and HIV topics, has been shown to increase discussions on dual protection and provision of condoms during regular family planning visits.<sup>86,96</sup> A screening tool developed by the Population Council and used by both receptionists and providers has also been shown to be effective in increasing the number of services accessed per visit.<sup>47</sup>

## Conclusion

Integration of services is clearly more complex than may often seem the case, and requires careful assessment and planning to identify the most effective and cost-effective service configurations to address the different components of SRH care. While this chapter has outlined a range of service models and strategies that can be considered, it is important to emphasize that integration may not always be the best solution for certain populations or certain health problems. Conceptually, sexual health and reproductive health are two overlapping areas, but neither fully incorporates the other. As has been noted, there may also be strong cultural differences between the two subspecialties that must be addressed before trying to integrate them.

Integration does not necessarily mean that vertical service delivery and specialist disciplines will be abolished. STI programs will continue to require specialized units at secondary or tertiary levels to provide comprehensive laboratory services for testing and diagnosis, and for the treatment of complicated STI and HIV problems. This can be maintained while integrating treatment services at the PHC or secondary level. Some key target populations for STI control (e.g., men, adolescents, and sex workers) may also continue to require more specialist units due to social barriers accessing care. The implication is that referral systems between primary and specialized facilities would need to be established or strengthened, and maintained. Depending on the sociocultural context, it may also be more appropriate to address certain problems in more specialist services; care for the victims of VAW being a typical example. A symbiosis of vertical and integrated approaches is therefore recommended.

Lastly, it is worth noting that settings with a strong foundation of government-funded primary care have more success with integration than those where donor-funded vertical programs



predominate.<sup>76</sup> Therefore, one of the first steps to delivering effective integrated STI and SRH services is to ensure that PHC services are strong. Programers then need to consider the different challenges to integration that we have identified here, and develop appropriate strategies to overcome them.

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# Monitoring and Evaluating Sexually Transmitted Infection Control Programs

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# 20

## Introduction

Monitoring and evaluation are fundamental components of health programs.<sup>1–4</sup> Through these processes, program managers at all levels of the health system are able to monitor progress towards national and international goals and commitments, take corrective actions to ensure programs meet their goals, develop concrete plans based on needs, and inform program strategies.

Within the context of national STI programs, monitoring and evaluation (M&E) are critical to program strengthening, and their close epidemiological and biological ties with HIV have increased the attention paid to monitoring and evaluation of these services. However, M&E of STI control programs should stand on the merit of STIs alone as a public health priority. Emerging issues of public health concern such as the evolving resistance of *N. gonorrhoeae* to most known antibiotics put further emphasis on the need for functional systems to be in place in order to allow governments to respond to such a serious health threat.<sup>5–8</sup> This means that the traditional effects of STIs among the population could become even more serious. STIs are among the most common and curable diseases. They are recognized as a major cause of reproductive and psychological morbidities as well as facilitators of HIV transmission.<sup>9,10</sup> Fragmented and low quality program delivery and monitoring have often resulted in data being under-reported and under-utilized<sup>11,12</sup>; this in turn has resulted in limited tracking of emerging issues such as resistance. The alarming rise in resistance among some STIs to many classes of antibiotics and the absence of new medications in the pipeline mean that the health burden of STIs could significantly rise.<sup>7</sup> This rise would most likely affect developing nations more severely. It is estimated that 340 million cases of curable STIs occur per year; these include syphilis, gonorrhea, chlamydia, and trichomoniasis. Most of these occur in South and South East Asia, with sub-Saharan Africa following and finally Latin America. In total, STIs account for 17% of economic losses due to ill health.<sup>13–15</sup>

What makes monitoring and evaluating STI programs so difficult is that many infected individuals are asymptomatic, particularly among women.<sup>15</sup> This results in a gross under-reporting of cases. Compounding this is that proper diagnosis

requires a pelvic and/or rectal examination, which means that clinical settings must have access to a number of additional commodities and infrastructure such as lighting, sterilization, specula, anoscopes, and trained staff,<sup>11,15</sup> to name a few. The lack of rapid and inexpensive tests that can be used in resource-poor settings further complicates appropriate diagnosis and management.<sup>15</sup> Given that the burden of STIs is mostly in developing countries that are under-resourced in terms of commodities and human capacity, it is not surprising that most STI data are limited and so underestimate the disease burden. Those data that are available are often of questionable value and not representative of the general population.<sup>11</sup> Even with additional material resources however, there are still issues related to human capacity which must be addressed in order to improve monitoring and quality assurance within programs.<sup>16</sup>

Monitoring and evaluation have gained a renewed interest from the international community, not only for the public health issues mentioned above but also as a result of performance-based funding.<sup>17,18</sup> Increasingly, donors are requiring governments to demonstrate their performance in order to benefit from international assistance, and this implies that relevant data must be available.

In this chapter, we will focus on monitoring and evaluating STI programs. Often this is discussed within the context of national HIV program M&E but in this chapter we will focus solely on STIs. We will define monitoring and evaluation; present indicators for programs at the national and sub-national level and conclude with a discussion on how resulting data can be used at all levels of the health system (Box 20.1).

## Defining Monitoring and Evaluation

Monitoring and evaluation serve different functions within disease control programs. Together, monitoring and evaluation help program implementers to<sup>19</sup>:

- Determine the extent to which the program is on track and to make any needed corrections accordingly.
- Make informed decisions regarding operations management and service delivery.



**Box 20.1** Components of a Monitoring & Evaluation (M&E) System\*

**People, partnerships, and planning**

1. Organizational structures with M&E functions.
2. Human capacity for M&E.
3. Partnerships to plan, coordinate, and manage M&E systems.
4. National M&E plan.
5. Annual costed M&E work plan.
6. Advocacy, communications, and culture for M&E.

**Collecting, verifying, and analyzing data**

7. Routine monitoring.
8. Surveys and surveillance.
9. National and sub-national databases.
10. Supportive supervision and data auditing.
11. Evaluation and research.

**Using data for decision-making**

12. Data dissemination and use.

\*Adapted from references 20 and 21.

- Ensure the most effective and efficient use of resources.
- Evaluate the extent to which the program is having or has had the desired impact.

For STI programs, the goal of M&E should be to ensure that services are proficient in the care and prevention of STIs in terms of quality and coverage.<sup>22</sup> This implies a need to ensure that programs

are of a standard that results in efficient patient management and that services are provided to those who need them.

Indicators are used to measure progress and these are often represented in a simple input-output-outcome-impact framework (Fig. 20.1). Indicators used in monitoring and evaluation should be:

- **valid:** they measure the condition or event they are intended to measure.
- **reliable:** they produce the same results when used more than once to measure the same condition or event.
- **specific:** they measure only the condition or event they are intended to measure.
- **sensitive:** they reflect changes in the state of the condition or event of interest.
- **operational:** they can be measured with developed and tested definitions and reference standards.
- **affordable:** the cost of measuring the indicators is reasonable and within the program's financial capacity.
- **feasible:** the approach to measure the indicators is possible within the context of the program.<sup>23</sup>

Selecting the most appropriate indicators means taking into account the above standards as well as considering the program's overall goals and objectives. Objectives need to be "SMART", that is: specific, measurable, achievable, reasonable, and time-bound.<sup>9</sup>

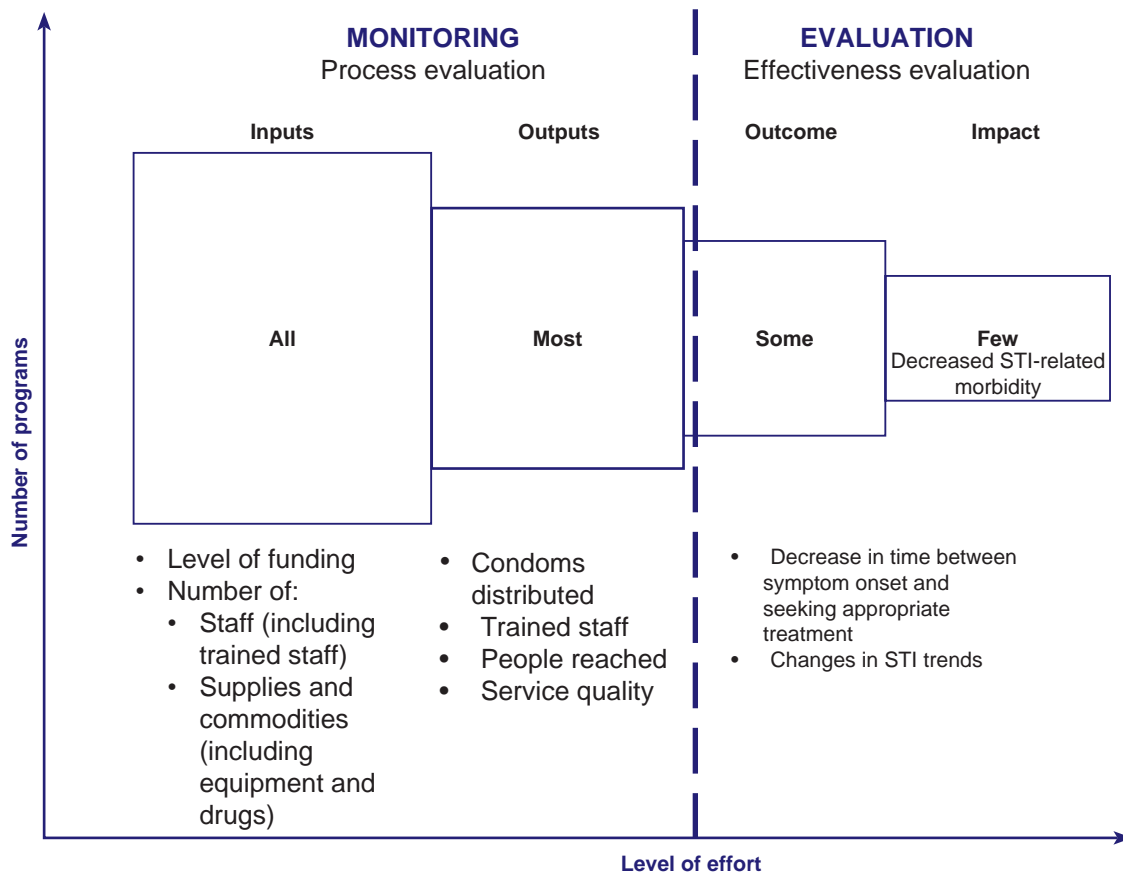


Fig. 20.1: Framework of monitoring and evaluation indicators.<sup>11,22,23,26,31</sup>

When developing STI program objectives, it is important to consider the components of a strong public health response. These include:

- Promotion of safer sex.
- Promotion of early healthcare seeking behavior.
- Introduction of prevention and care in all primary healthcare programs (including reproductive health and HIV).
- A comprehensive approach to case management that encompasses: identification of the disease/syndrome, antimicrobial treatment, education and counseling, promotion of correct and consistent condom use, and partner notification.<sup>13</sup>

Together, these components contribute to an STI control program's goals which should include reducing the rate of exposure (decreasing sexual partners and prevalence), reducing the efficiency of transmission (through safer sex behaviors such as using barrier methods such as condoms), and reducing the duration of infectiousness (through early treatment).<sup>22</sup> The identification of a program's goals and objectives is usually part of the program planning process; the indicators and processes related to the collection, management, reporting, and use of data are usually included in an M&E plan. When selecting indicators, a good rule is to collect only what will be used.<sup>24</sup>

Monitoring is defined as the routine tracking and reporting of priority information about a program and its intended outputs and outcomes.<sup>25</sup> Monitoring is a routine, or on-going, activity which aims to answer the questions "what are we doing?", "to what extent are planned activities actually realized", and "was the quality of planned activities satisfactory?"<sup>19,26</sup> Monitoring usually measures progress through the use of input and output indicators.<sup>11,23</sup> At the facility level, this generally involves keeping track of the number of people seen and treated in clinical logbooks which can then be tallied and sent for higher-level reporting. At this level, the number of indicators needing to be reported should be limited, as the clinical sites are also collecting individual patient information that is used for patient management. This means that there is a heavy recording burden at the clinic-level which can compromise data quality and use if too many data are required to be reported routinely.

At the minimum, program monitoring should include measures of:

- service delivery: number of clients served, pregnant women screened and treated for syphilis, condoms distributed, individuals referred for voluntary counseling and testing for HIV.
- quality of care: proportion of clients treated according to national (or international, in the absence of national guidance) guidelines; emerging resistance (including monitoring for treatment failure and trends in antimicrobial susceptibility).
- adequacy of staffing: patient load.
- patient response and satisfaction: total number of clients served; initial vs. repeat visits.
- capital and recurrent program costs: assess efficiency and cost-effectiveness.<sup>13</sup>

In practice, monitoring should include not only input and output indicators but measures of service quality and coverage as well. The latter two monitoring practices require periodic special studies that include provider interviews, direct observation of provider and client interactions, the use of mystery clients, reviews of clinical records, and patient exit interviews or surveys.<sup>22,24</sup>

Evaluation is defined as the rigorous, science-based collection of information about program activities, characteristics, and outcomes that determine the merit or worth of a specific program.<sup>11</sup> Unlike monitoring, evaluation occurs at specific times, usually once a program has been up and running for a specified period of time when anticipated intermediate outcomes could be expected. This is generally done in programs that are 3–5 years old<sup>27</sup>; it would be anticipated that most people for whom the services were intended would have been exposed to the program by then, making it feasible to evaluate the program outcomes. While evaluation is most often carried out at the national level to evaluate the overall response, there is also a role for evaluation at the sub-national level. At this level, evaluation is specific to the services being implemented at a site or group of sites. It focuses on the scope (what was done), the scale (what was the program's coverage), and quality. In these situations, indicators that are tailored to the activities or interventions in place are used; this differs from national-level evaluation where more standard indicators are used.<sup>26</sup>

Evaluation aims to determine whether programs are successful and how well they are achieving their overall goals and objectives. The purpose of evaluations is to influence decisions. The complexity and level of rigor of an evaluation should be based on who are the decision-makers to be influenced and the types of decisions that need to be made.<sup>27</sup> Evaluation requires an approach which looks at coverage among the population to the intervention(s), identifying those nonintervention related factors that affect outcomes, and measures of behavioral and biological outcomes.<sup>11,27</sup> Evaluation differs from research aimed at proving the efficacy or effectiveness of an approach, such as the studies that sought to demonstrate how STI control might reduce HIV incidence<sup>12</sup> or those that have demonstrated innovations in STI control program monitoring.<sup>28,29</sup> Once research demonstrates effectiveness, then these components are usually integrated into programs; these in turn are then evaluated at the national level to determine how well the response has resulted in overall reduction in STI prevalence and incidence.

Good evaluations use a mix of indicators appropriate for the different levels of the program, a combination of qualitative and quantitative approaches, and participatory approaches to design the evaluation plan.<sup>26</sup> There are several different types of evaluations including formative, process, and effectiveness (impact) evaluations. Cost-effectiveness evaluations are also important and are discussed in more detail in a later section. Process evaluations assess to what extent the planned intervention activities actually are being implemented. They assess what services are being provided, to whom, when, how often, and for what duration. Effectiveness and impact evaluations assess whether

the program made a difference. At the beginning of a program cycle, a formative evaluation (also called a formative assessment) can be done in order to collect information on the current situation in order to identify gaps and inform STI control program designers.<sup>22,30</sup>

At the national level, evaluation aims to assess the country's overall response. National-level evaluations often use surveillance data as a tool and a standard set of internationally agreed-upon indicators that allow comparability across regions and countries. The most common type of evaluation that occurs at this level is an effectiveness or impact evaluation. This type of evaluation relies heavily on biological and behavioral indicators<sup>30</sup> which are often collected as part of a country's surveillance system.

At the sub-national, or site level, evaluations are more specific to the actual activities being undertaken in that area. At this level, process evaluations are more common and these types of evaluations rely heavily on input (e.g., staff, commodities, and funding) and output (e.g., number of people treated) indicators (Fig. 20.1).

### SUB-NATIONAL LEVEL MONITORING

At the sub-national level (clinical facilities, districts, and regions), monitoring data focus mostly on monitoring a program's inputs and outputs (for example, funding, staff and people reached). The data gathered here meets three main aims: to monitor service delivery (how many people were diagnosed and treated), staff performance (are providers diagnosing and treating in line with national guidelines; what is the workload on staff), and quality of services (are people being treated effectively and with respect). These data are used to track progress towards targets but they also play an important role in ensuring that services are of good quality and respond to client needs.

At the sub-national level, healthcare facilities collect information using a wide range of tools such as patient registries, laboratory logbooks, and supply management registers. In most resource-constrained settings, data are collected on paper forms, and then consolidated into either summary (paper) forms or into electronic databases. These summary data are sent to the district level (or administrative equivalent) where they are again consolidated (with data from all facilities under the district's supervision) and sent further up the health system hierarchy. This process makes up a country's health management information system (HMIS) and serves as the backbone to inform management decisions and track progress being made at all levels of the health system.

There are several monitoring activities that take place at this level<sup>9</sup> (Table 20.1):

- Regular (monthly or quarterly) summary activity reports (from a facility to the district level, and from the district level to higher levels in the health system).
- Monthly financial reports.
- Feedback/monitoring meetings (from the facility to staff, and from the district to the facilities).
- Site visits (often as part of supervisory visits from the district to facilities).

**Table 20.1:** Examples of Common Questions, Indicators, and Data Sources for Sub-National Level Monitoring<sup>9,23</sup>

Monitoring question	Monitoring indicators	Data source(s)
Are activities carried out as planned and in a timely fashion?	Number of activities being implemented as planned	Program records
Have targets been met?	Number of people served (by age, sex)	Clinic records
How many people have been reached by the services?	Number of people served (by age, sex)	Clinic records
How many service providers have been trained in STI management?	Number of service providers trained	Program records
Is there an adequate and appropriate drug supply?	Number of drugs dispensed; number of drugs left in inventory at the end of the month; drug stockouts in the last 3 months	Commodity registers
Are the costs of the program within budget?	Expenditure vs. budget analysis	Financial records
What are the rates of specific STIs being treated?	Number of people served, by STI diagnosis	Clinic records
Is there a commodity management system in place?	Number of condoms distributed	Clinic records

- Training sessions (for all staff in facilities).
- Data analysis and management (often done at the district level, with feedback to facilities).
- Report writing and dissemination (a summary report, either paper or electronic, is compiled at the facility level; the district then compiles a similar report with summary data from all the facilities under its authority).
- Review of drug and commodity inventories (at the facility and district levels, to ensure all essential drugs are available).

As mentioned previously, an important monitoring function at the sub-national level is to monitor the quality of services, including staff performance. Unlike other monitoring data, collecting information on service quality requires that facilities and districts plan and carry out special exercises that allow for the collection of these data. Table 20.2 summarizes some of the common approaches used to collect information on service quality. At the clinic level, these exercises should inform a quality improvement process; that is, the data collected are used at this level to plan for and implement changes which will result in a stronger program.

### NATIONAL LEVEL MONITORING

Monitoring at the national level is focused around collecting, managing, and synthesizing data that come from the sub-national level and which can be used to track overall national program

**Table 20.2:** Methods to Monitoring and Assessing Program Quality and their Advantages and Disadvantages<sup>22,23</sup>

Method	Advantages	Disadvantages
Provider interviews	<ul style="list-style-type: none"> <li>• Relatively easy to carry out</li> <li>• Permits evaluating a range of knowledge</li> <li>• Standardized protocols exist</li> </ul>	<ul style="list-style-type: none"> <li>• Reporting bias</li> </ul>
Direct observation of provider	<ul style="list-style-type: none"> <li>• Transparent</li> <li>• Standardized protocol exists</li> </ul>	<ul style="list-style-type: none"> <li>• Difficult and expensive</li> <li>• Observation bias (observed provider may act differently than when not observed)</li> </ul>
Mystery client	<ul style="list-style-type: none"> <li>• Can be less expensive than provider observation</li> <li>• Less likelihood of observation bias</li> </ul>	<ul style="list-style-type: none"> <li>• Possible negative reactions to providers being observed</li> <li>• Mystery client may not have the actual clinical signs that may affect the way they are managed</li> <li>• Ethical concerns, e.g., wasting providers' time which could be used to provide real services; lack of informed consent by providers</li> </ul>
Record review	<ul style="list-style-type: none"> <li>• Avoids some observation bias</li> <li>• Less costly</li> </ul>	<ul style="list-style-type: none"> <li>• Information in records can be limited and is often inconsistent</li> </ul>
Patient exit interviews	<ul style="list-style-type: none"> <li>• Can be less expensive than direct observation</li> <li>• Less likelihood of observation bias</li> </ul>	<ul style="list-style-type: none"> <li>• Recall bias (patient may not accurately remember details of clinical procedures of counseling messages)</li> </ul>
Client satisfaction surveys	<ul style="list-style-type: none"> <li>• Can be less expensive</li> <li>• Less likelihood of observation bias</li> </ul>	<ul style="list-style-type: none"> <li>• Selection bias (those clients who select to fill in the survey may be different from other clients)</li> <li>• Recall bias (patient may not accurately remember details of clinical procedures of counseling messages)</li> <li>• Previously dissatisfied clients do not return to service and will not be sampled</li> </ul>
Quality assurance checklists	<ul style="list-style-type: none"> <li>• Relatively easy to carry out</li> <li>• Standardized protocols exist</li> </ul>	<ul style="list-style-type: none"> <li>• Requires subject matter experts to administer</li> </ul>

performance. At the national level, significantly smaller pieces of information are collected, and their availability reflects the overall function of the HMIS. These data are used to identify potential gaps in the response and inform new national plans and policies. They are used also for reporting against international goals such as the Millennium Development Goals and the UNGASS Declaration of Commitment (Table 20.3).

**Table 20.3:** Examples of Common Questions, Indicators, and Data Sources for National Level Monitoring<sup>9,23</sup>

Monitoring question	Monitoring indicators	Data source(s)
Have targets been met?	Cumulative number of people served (by age, sex)	Program records
How many people have been reached by the services?	Proportion of target population reached	Routine reports, census data, special studies
How many service providers have been trained?	Proportion of health workers trained in STI case management	Program records
Is there an adequate and appropriate drug supply?	Proportion of health facilities reporting a drug stockout in the previous 3 months	Facility survey
What are the rates of specific STIs being treated?	Proportion of clients presenting for STI management who are treated according to national guidelines	Program records, facility survey

## Evaluation

Program evaluation can occur at any level, but this depends on the purpose of the evaluation. In a previous section, we mentioned that there are generally three types of evaluation: formative, process, effectiveness (impact). The differences between these and the questions that they answer are presented in Box 20.2. At the sub-national level, evaluation can be used to assess a new approach, which can then be scaled up if found to be effective. Within the context of STI control programs, national level evaluations are relevant as they can answer the questions “What have we achieved?” (or “What outcomes are observed?”) and “What impact have we had?” (or “Does the program make a difference?”).<sup>9,19</sup> As previously mentioned, a program can be evaluated once it has “matured”, at this time it can be expected that the program has reached the majority of people it should have, hence the data needed will then be available to see if the program has achieved its outcomes and expected impact. Evaluations generally occur anywhere from 3–5 years after implementation.<sup>27</sup>

Evaluations use a mix of qualitative and quantitative methods to measure core outcome and impact indicators; surveillance also plays a key role. These indicators measure changes in societal attitudes, knowledge, and behaviors; changes in the prevalence and incidence of, as well as morbidity associated with STIs; and the overall response in terms of changes in funding and policies.<sup>26,32</sup>

There are some key limitations to the evaluations of STI control programs as these programs cannot be evaluated using traditional research approaches.<sup>26,33,34</sup> Often no baseline is available



Box 20.2 Different Evaluation Types and Examples of the Questions they Answer <sup>22</sup>	
Evaluation types and their uses:	Examples of questions that are answered by the different evaluation types:
Formative evaluation (to inform program design)	Is a program needed? Who needs the program? How should the program be carried out?
Process evaluation (monitoring overall inputs and outputs; assesses service quality)	To what extent are planned activities actually being realized? How well are the services being provided?
Effectiveness or impact evaluation (assesses outcomes and impact)	What outcomes are observed? What do the outcomes mean? Does the program make a difference?
Cost-effectiveness evaluation	Should program priorities be changed or expanded? How should resources be reallocated?

**Table 20.4:** Examples of Common Questions, Indicators, and Data Sources for National Level Evaluation<sup>22,23,26</sup>

Evaluation question	Evaluation indicators	Data source(s)
What outcomes were observed?	<ul style="list-style-type: none"> <li>Improved treatment seeking for STIs</li> <li>Prevalence and incidence of selected STIs (e.g., gonorrhea or urethral discharge syndrome) among men in past 12 months</li> <li>Prevalence of syphilis in women attending antenatal care services</li> <li>Prevalence of STIs in various sub-populations</li> <li>Decreases in symptom duration</li> </ul>	<ul style="list-style-type: none"> <li>Behavioral surveys/clinic data</li> <li>STI surveillance, STI studies</li> </ul>
Does the program make a difference?	Decreases in STI-related morbidity.	STI surveillance and clinical data, facility survey, behavioral surveillance survey (with or without biological markers)

to compare the situation before and after and, because most programs target the entire population, there are no control groups which would allow comparisons of the differences in terms of STIs between those who benefited from the program and those who did not. Additionally, the evaluation of a national program is often unable to attribute its effect to any one response, particularly in environments where multiple programs exist and overlap (as may be the case in countries where nongovernmental organizations are implementing programs). Finally, a large sample size is required to measure changes in STI prevalence which makes these evaluations expensive especially where biological markers

are needed (i.e., presence of an STI) to complement self-reported behaviors (which are prone to recall and social desirability biases).

## COST-EFFECTIVENESS EVALUATIONS

Limited resources for STI programs make selecting program components that maximize improvements in health at minimum cost an important concern. Economic evaluation aims to assure that program components and strategies are selected in a way that puts resources to their most valuable use. Evidence from cost-effectiveness analysis (CEA), the main approach to economic evaluation in health,<sup>35</sup> underlies many of the program components recommended by WHO's Global Strategy for STI Prevention and Control.<sup>36</sup> Recommendations regarding standard methods for conducting CEA for health and medical interventions have been developed by the U.S. Panel on Cost-Effectiveness in Health and Medicine, more recently the World Health Organization<sup>37</sup> and also by UNAIDS<sup>38</sup> specifically for HIV interventions. Chiou<sup>39</sup> provides a grading system for assessing CEA studies in health, which mainly focuses on methodological issues expressed in the guidelines and transparency in reporting results.

The process of developing a CEA can provide valuable insight beyond the final cost-effectiveness findings. Carrying out a CEA, the process of developing a CEA can provide valuable insight by obliging planners to clearly define resources needed to carry out an intervention, characterize the potential impacts, their value and consider which population groups would benefit and which would bear the cost; thus the CEA exercise can therefore serve to clarify objectives as well as revealing key assumptions regarding the mechanisms through which health improvements will be achieved and identify key areas of uncertainties. For example, for many interventions, levels of service regarding utilization of the services provided as well as effect or the size and or duration are not well-understood but are highly influential on CEA findings of effect.<sup>35,40</sup> As yet, although there is a growing knowledge base of CEA studies, particularly for HIV<sup>41</sup> and other STIs such as Human Papillomavirus (HPV) where new vaccines have stimulated interest in cost-effectiveness,<sup>42–45</sup> economic evaluations are still not available for many common interventions, such as behavior change communications for persons with HIV, school-based HIV prevention, abstinence programs, and prevention with most-at-risk populations in concentrated HIV epidemics, to name a few.<sup>41,46</sup> Many other interventions have evidence from only one or a few studies or countries.<sup>41,47</sup> Furthermore, CEA is seldom used by national STI control programs in decisions to adopt, scale up or eliminate program components, so that such choices are often not based on evidence of how health can be most improved with available resources available. Although crucial, cost-effectiveness is rightly viewed as just one input to STI programming decisions, along with, and secondary to, feasibility, appropriateness, acceptability, sustainability, synergies with other health programs and ethical considerations. Even under the narrow lens of economic considerations alone, Creese et al.<sup>47</sup> point out that, beyond determinations of what services

should be offered by the public sector, there are many relevant factors beyond cost-effectiveness, such as demand for services, affordability, and availability of insurance to cover the same services.

## Cost-Effectiveness Ratios

Most economic evaluations in health produce a cost-effectiveness (CE) ratio, which is expressed as a measure of benefits (i.e., health improvements) resulting from the intervention relative to the intervention's total cost ( $B/C$ ). CE ratios thus represent the health return on investment in an intervention compared with taking no action (the *null*). In contrast, *incremental cost-effectiveness ratios* (ICERs) directly compare two interventions by dividing their difference in benefits by their difference in costs, i.e.,  $(B_2 - B_1) / (C_2 - C_1)$ . WHO recommends that all studies provide CE ratios relative to the *null*, to allow comparability across studies, in addition to any ICERs presented against specific alternatives.<sup>37</sup> Both ratios reflect health benefits per unit investment (e.g., infections prevented per \$); however, this relationship can be highly sensitive to the size of an intervention due to economies of scale in costs and nonlinear epidemic dynamics. For example, the scale of HIV prevention programs explains 26–70% of cost variation across locations for similar interventions, with average cost either increasing or decreasing with the volume of services depending on the type of intervention and level of coverage.<sup>48</sup> Thus, how interventions compare with one another may differ depending on the budget available for implementation; in practice, planners should compare *net benefits* ( $B - C$ ) at scale when deciding between STI control and prevention strategies.<sup>40</sup>

## Cost Considerations

Many choices must be made when deciding what costs should be included in a cost-effectiveness analysis. All major guidelines for CEA in health and STIs<sup>35,37,38</sup> embrace the social welfare framework, which calls for accounting for all societal resources consumed by an intervention as well as all benefits resulting from the intervention. This orientation is known as the *societal perspective*. In practice, many CEAs of STI interventions take a more limited view by considering only *direct costs*. For screening or treatment services, direct costs would include personnel, equipment, medications and vaccines, diagnostic tests, physical infrastructure, overhead, as well as patient and partner travel to access services, treatment of partners and partner tracing for partner program management services. In prevention of mother-to-child HIV transmission interventions, the cost of treatment of newborns is also relevant.<sup>49,50</sup> Costs of promotion, advertising, outreach, and incentives to patients, if relevant, should also be included, as in hepatitis B virus immunization of IDUs,<sup>51</sup> or mass prevention and screening campaigns.<sup>52</sup> Additionally, costs arising from the negative health consequences of an

intervention should be considered; for example, evaluations of antenatal screening for herpes simplex virus must account for the cost associated with unnecessary cesarean deliveries.<sup>53,54</sup> *Indirect costs*, including productivity losses associated with time spent accessing services or with complications resulting from untreated infections,<sup>45,55–61</sup> are relevant to the societal perspective, but with notable exceptions,<sup>49,50,52,62</sup> most CEA of STIs do not account for them. Yet indirect costs can vary across interventions: treatment or STI management programs often require multiple consultations while a one-shot condom distribution campaign would likely consume less of participants' time. Unique among CEA guidelines, WHO advises against including patient time costs, unless they are thought to be substantial, such as in the case of accessing chronic care.<sup>63,64</sup> Thus, differences among the guidelines may explain variation in CEA methods in this respect, and limit comparability across HIV and STI cost-effectiveness studies as pointed out by recent reviews.<sup>41,45</sup> Finally, *intangible costs*, such as pain and anxiety associated with treatment side effects,<sup>37</sup> are rarely considered.

## Impact Considerations

STI programs can influence health outcomes on multiple levels, from quality of life improvements among individuals treated to averted infections and disability in newborns, partners, partners of partners, and so on. However, in practice, there is a great deal of variation in what health benefits are considered in CEA as well as how they are measured. For example, some studies of HPV immunization explore how services may impact HPV prevalence, incidence of genital warts, and cervical cancer.<sup>43</sup> Studies of screening and alternative diagnostic algorithms have examined STI cases detected or treated,<sup>43,63,65–67</sup> as well as cases of infertility, ectopic pregnancy, perinatal death or spontaneous abortion averted,<sup>66–69</sup> or simply the number of tests or correct treatments conducted.<sup>50,70</sup> In studies of HIV, the number of HIV infections prevented is often the principle outcome<sup>61,71,72</sup>; however TB cases averted and life expectancy have also been used.<sup>41,61</sup> Such variations make it difficult to assess which interventions produce most health value. Thus, the standardized summary measures of quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs), which account for years lost to premature death and years lived at different health states, are recommended,<sup>35,37,73</sup> although less frequently used.<sup>38,52,55,56,58,59,74–78</sup> When QALY or DALY measures are available to compare CE across interventions, “rule-of-thumb” thresholds are often applied, such as considering a cost below US\$50,000 per QALY cost-effective in the United States. Investigations of the value-of-life literature, however, suggest that this threshold could either overstate<sup>79</sup> or understate<sup>80,81</sup> true societal preferences for willingness to pay for health improvements. WHO recommends that interventions with a cost per QALY below the per-capita gross domestic product (GDP) be considered cost-effective.<sup>82</sup>

## Timing Considerations

Different interventions will result in different rates of costs and health benefits over time. For instance, a prevention media campaign may require a large initial investment and eventually prevent infections only some time after the intervention has been implemented, while a mass STI screening and treatment campaign is more likely to generate substantial health benefit immediately. Thus, to facilitate comparison of interventions, both costs and benefits should be expressed in *present-value* terms, with costs and benefits occurring in the future *discounted* to account for time preferences. A discount rate of 3% annually is a standard for economic evaluations in health with a reasonable range of 5–7%.<sup>35,37</sup> While CEA of STI and HIV interventions typically discount at these rates, they differ widely in their approach to analyzing the full stream of impacts over time. WHO recommends estimating all costs and benefits resulting from at least 10 years of full program implementation, noting that these impacts may extend well beyond the implementation period.<sup>37</sup> Yet, in practice, arbitrary time horizons such as 1 or 5 years following the intervention under examination are often used.<sup>37,50,59,83,84</sup> Some studies limit their time horizon more severely to completion of a diagnosis or treatment episode.<sup>61,68,72</sup> At the other extreme, more comprehensive analyses consider impacts over the lifetime of program participants. This is more often the case in evaluations of immunization, screening, or treatment interventions. Deogan<sup>52</sup> provides a rare example of a 30-year time horizon appropriately justified based on the duration of STI symptoms. Studies that do not capture the full impact of an intervention by employing a sufficiently long time horizon may claim to present a conservative analysis, but they do so at the expense of potentially underestimating efficiency in generating health improvements, thus departing from the social welfare framework and complicating comparisons of cost-effectiveness findings.

## Estimation Approach

Choice of estimation approach can also influence the extent to which costs and benefits are fully accounted for. Empirical approaches track data on participants during actual implementation, such as in Smith's<sup>70</sup> comparison of clinic- versus home-based STI screening using data from a randomized control trial. The relative cost-effectiveness of different STI diagnostic strategies is often estimated by applying multiple diagnostic algorithms onto a single group of patients presenting to a clinical setting for care and tracking correct diagnoses, treatments, and associated costs.<sup>58,68,70,85</sup> However, more often, a mathematical model is needed to combine what is known regarding epidemiological context, disease progression, intervention efficacy, behavioral parameters and other relevant information in order to project out costs and averted infections beyond what has been observed empirically. For example, Postma<sup>50</sup> used data on chlamydia prevalence, complication rates from cohort studies, diagnosis and treatment rates for STI patients and partners,

number of partners and transmission probabilities per sexual contact, reinfection rates in the absence of treatment and other parameters to estimate the cost-effectiveness of treating male partners of women screened for chlamydial infection. The most common model in CEA of STI programs is the decision tree, which defines a sequence of possible outcomes (e.g., cured vs. not cured) or states (e.g., infected vs. not infected) as “branches” over which probabilities and associated intervention outcomes are computed. Decision trees are frequently used in comparing diagnostic and treatment strategies.<sup>50,66–68,77,86,87</sup> Markov models, which define probabilities of transition between a set of mutually exclusive and exhaustive health states, are also common, for example to analyze the cost-effectiveness of routine HIV testing in the US,<sup>56</sup> viral hepatitis immunization of IDUs<sup>51</sup> and HPV screening.<sup>88</sup> Yet, all of these methods—empirical, decision trees, and Markov models—are generally unable to capture perhaps the central feature of infectious disease control: the ability of an intervention to influence population prevalence of infection by reducing infections from the population through prevention or treatment (i.e., *herd immunity*). As interventions expand, this effect can be quite powerful and can contribute to cost-effectiveness. For example, White<sup>89</sup> showed that by expanding STI diagnostic and treatment services in Britain, demand for those services would eventually decrease over time due to averted infections in sex partners of treated patients, as well as lower reinfection rates in among those treated, so that services levels could in time be reduced, forming a “virtuous circle”. *Dynamic* models—simulations,<sup>43</sup> compartmental,<sup>90</sup> and hybrid models<sup>91</sup>—can account for such effects by allowing prevalence to adjust with intervention impact.<sup>69,92</sup> However, dynamic models typically require additional data and assumptions regarding disease transmission, and perhaps for this reason comprise only a minority of CEA studies<sup>41,93</sup>; their use does appear to be growing in CEA of HPV vaccines.<sup>45</sup> As in the case of limited time horizons, estimation methods that limit consideration of impacts by failing to account for herd immunity essentially “short-change” the intervention in question by underestimating its contributions to health. As most CEA models in STIs use a static, rather than dynamic, approach, it is likely that the economic efficiency of STI interventions relative to other health interventions may be systematically undervalued through cost-effectiveness comparisons. Marra and colleagues<sup>43</sup> provide an excellent comparison of methods and assumptions used in HPV screening CEAs. More generally, Weinstein et al.<sup>94</sup> discuss the proper use of mathematical modeling for health interventions.

## Program Data for Cost-Effectiveness Estimation

Evidence regarding cost-effectiveness of STI strategies in low- and middle-income countries is scarce, although critical at both the international and national levels to guide program decisions. The WHO's Choosing Interventions that are Cost-Effective (CHOICE) initiative provides up-to-date information on



estimated costs, health impact in DALYs and cost-effectiveness of priority health interventions, which can be calibrated to specific country contexts.<sup>37</sup> Nonetheless, as the CHOICE estimates are only as good as existing evidence, STI programs should attempt to collect the necessary data to document cost-effectiveness and report estimates to improve the evidence base. At a minimum, data collected should include direct costs to the program and participants, as described above, participants' time in accessing program services to permit calculation of indirect costs and program outcomes on health and behaviors. Coupled with epidemiological data, such information can then be used to estimate total health benefits and cost-effectiveness.

## Objections to CEA in Health

Objections to CEA arise often. Neumann<sup>95</sup> suggests that in the US, there is a mistaken perception of economic evaluation as being similar to "healthcare rationing"; detractors perceive CEA as an attempt to limit provision of services when, in fact, the motivation is to get the most out of them. Others may reject the notion of collective priority-setting as wresting control from individual doctors and patients. Opponents of CEA may also simply dislike limits or the very idea of acknowledging trade-offs, which CEA attempts to make as explicit as possible to encourage informed decisions. Finally, the societal perspective can seem unrealistic compared to the real-life institutional interests faced by decision-makers.<sup>95</sup> However, Williams<sup>96</sup> argues that, while there is no perfect way to distribute limited health resources, CEA using QALYs is an attractive option. Summary health measures such as QALYs and DALYs have also been the subject of considerable ethical debate, on the grounds that measuring the value of health states cannot be done well, that utilitarianism is unethical, that such measures favor improving health in younger versus older individuals and those without versus with disabilities and out of concern that these measures intended for collective prioritization may be inappropriately utilized by physicians in clinical care.<sup>96</sup> Additional ethical perspectives on QALYs and DALYs can be found elsewhere.<sup>97–99</sup>

## The M&E Plan

An M&E plan ensures that sufficient resources are allocated to M&E activities (in terms of time, money, and human resources) to ensure that data are used in decision-making processes; and to ensure that an evidence base is created and used to demonstrate progress towards program objectives and goals. Because of the participatory process required to develop these plans, they also serve to create a culture of data demand among program planners; by participating in the M&E planning process, individuals understand the need for data and are more inclined to use it for future decision-making.<sup>19</sup> The plan should describe, in detail, both the organization and activities related to M&E including roles and responsibilities at all levels of the health system, the baselines and targets to be achieved, methods of data collection, data sources, frequency of data

collection (and the partners responsible for data collection and management), and data analysis and data use at different levels of the system. In summary, M&E plans describe how each of the 12 components of the M&E system (see Box 20.1) will be implemented and/or strengthened within the context of a national disease control strategy or plan.<sup>21</sup>

Developing an M&E plan involves several steps. These are: (i) creation of an M&E working group made up of representatives of technical partners and stakeholders involved in the STI response; (ii) review of existing plans, projects, data and past evaluation studies; (iii) identification and prioritization of indicators and M&E approaches (which should take into account internal and external M&E resources and capacity); (iv) selection of indicators and data sources (which includes looking at their feasibility); (v) development of an M&E work plan and budget; and (vi) dissemination of the plan, often through a stakeholder meeting.<sup>23,100</sup>

## DATA USE

The ultimate use of M&E data has often been considered outside the scope of monitoring and evaluation and, therefore, it is often not given sufficient attention during the design and planning of monitoring and evaluation systems. This has led to gaps in countries between the data that were collected and those which were actually used to prevent the spread of disease or improve the lives of those affected.<sup>101</sup> In some cases, data needed to perform important program functions have not been collected. In others, data were collected but never used, for example, because the data were not available in the time or format in which they were needed or because the program lacked the human or physical resources required to use them effectively. Recognizing these gaps, data use is increasingly recognized as an integral part of a monitoring and evaluation system and should be highlighted within any M&E plan.

The purposes for which data are used, and the specific data that are required to support work, vary at different levels of the health system, and from country to country. In general, however, there are three categories of use: during the delivery of services at the point of care (i.e., the health center), for health facility management, and for health system management.<sup>102</sup>

## DATA USE AT THE CLINIC LEVEL

Many of the data that are used to monitor and evaluate STI services are routinely recorded during the delivery of STI services at the facility level. These data are stored and managed in the form of individual patient records, and primarily used to inform decisions about patient/client care as well as to allow for the quality assurance process. In addition, information about the availability and consumption of resources at the health center (such as records of pharmaceuticals and other supplies distributed and in stock) is also regularly reported upwards. This information is used to ensure that health centers have sufficient resources to continue providing services, and is compared with service delivery information to forecast future resource needs.



To minimize the amount of time that healthcare workers have to spend collecting data, and to promote the best quality data, it is recommended that data that do not have a use at the recording level should not be required for reporting.

### DATA USE AT THE SUB-NATIONAL LEVEL

Oversight of health facilities may take place at different levels of the healthcare system, depending on the organization of the health system and the degree to which management has been decentralized by the government.

Regardless of whether health facility management occurs at the district, regional, or national level, key indicators (derived from aggregated data reported by multiple health facilities) are used to measure the impact on STIs (e.g., the incidence and prevalence) and the effectiveness of STI services in the geographical or political area covered. These data are compared against data about the population of the area (such as the population size, and age/sex distribution) and other epidemiological indicators (such as the percentage of a population that is expected to be at risk) to determine the extent to which services are meeting population needs.

Such monitoring data are essential for evidence-based planning and evaluation of STI programs. Information about the impact of STIs and the effectiveness of existing services allows planners and managers to prioritize the populations and settings that should be targeted, plan appropriate STI program activities for each health facility; allocate resources, and set facility-specific and program-wise goals, objectives, and targets.

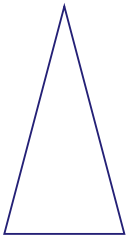
Data subsequently reported by health facilities allows managers to track the performance and improve the quality of these programs. Monitoring data are used to assess, verify, and demonstrate the success of interventions by comparing what actually happened to what was planned.<sup>103</sup> The evaluation of these data allows planners and managers to adjust programs to address weaknesses that have been identified (such as by reassigning responsibilities or reallocating resources) and to introduce and test improvement options for STI management within facilities, gradually improving the quality of services over time.<sup>17,104</sup>

These monitoring and evaluation data are used by health facility managers to highlight results and strategic lessons that can guide decision-makers and stakeholders in the overall health system.

### DATA USE AT THE NATIONAL LEVEL

Detailed information about the national STI program, including information about the populations covered by services, the resources budgeted and used, and the outcomes of STI interventions are typically aggregated at the national level.

These monitoring and evaluation data are used to inform national surveillance efforts and the national research agenda, as well as to support the management of finances at the national level. By tracking the flow of funds to service providers and other beneficiaries, and comparing them with data describing the impact

Level of data collection	Use	Data quantity
Global/Regional	Global reporting (UNGASS, MDGs)	
National	National planning and reporting	
Subnational	District planning and national reporting and planning	
Facility	Clinical team management, financial audits, and drug supply management	
Patient	Individual patient management	

**Fig. 20.2:** Monitoring and evaluation use and data quantity at different levels of the health system. UNGASS: United Nations General Assembly Special Session (on HIV/AIDS); MDGs: Millennium Development Goals.

of services, stakeholders and coordinating authorities are able to assess the cost-effectiveness of interventions and their relevance in meeting the priorities set by the national health system.

Such data are also used at the national level to demonstrate results, and areas of weakness, in support of advocacy campaigns and for mobilizing additional resources. In countries where performance-based financing has been implemented, such as in countries that have received loans from the World Bank or grants through the Global Fund to Fight AIDS, Tuberculosis and Malaria, demonstrating the outcomes of national programs is essential to sustaining the availability of health resources and maintaining services.<sup>18,105</sup>

Key indicators of the performance and impact of a national STI program are typically generated at the national level each year. In many cases, countries report data from STI programs annually to international agencies responsible for tracking progress towards achieving international goals (Fig. 20.2).

## Conclusion

Monitoring and evaluation are fundamental components of STI control programs. Within the context of decentralization and performance-based funding, as well as the increasing threat of gonococcal antimicrobial resistance, STI programs must have monitoring and evaluation systems in place that allow for the timely collection, management, and use of information.

While monitoring focuses on routinely measuring inputs and outputs, the collection of these data allows for service strengthening and may also contribute towards identifying emerging issues in a program. The added element of monitoring, measurement of service quality, allows for quality improvement processes to be put into place.

Evaluation, which is more periodic, involves the use of data from multiple sources. The complexity and expense related to carrying out a national level evaluation should be taken into account at the program planning stage in order to assure that resources are available to evaluate the medium-term outcomes or impact of the response.

## Summary

Monitoring and evaluation (M&E) are fundamental components of health programs. These activities help to inform program design, track progress being made, assure services are of the required quality, and measure the program's outcomes and impact. Emerging public health issues including antimicrobial resistance and an increased demand for data as a result of performance based funding require programs to revisit and strengthen their M&E efforts.

Monitoring and evaluation complement an STI control program's goals and objectives; they use indicators to track performance and measure change. These indicators can be broken down into an input, output, outcome and impact framework. Monitoring is defined as the routine (on-going) tracking and reporting of priority information about a program and its intended outputs and outcomes. Another important monitoring activity is measuring service quality.

Evaluation is defined as the rigorous, science-based collection of information about program activities, characteristics, and outcomes that determine the merit or worth of a specific program. Evaluations measure outcome and impact indicators. Unlike monitoring, evaluation occurs at specific times, usually once a program has been up and running for a specified period of time. Surveillance data play an important role in the evaluation of a program.

An M&E plan is needed in order to explain how the M&E system will work. These plans should include budgets to cover all M&E activities, clarify roles and responsibilities, and describe how data are managed, reported and used at all levels of the healthcare system.

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# section V

## BASIC AND LABORATORY SCIENCES

— *Jonathan Ross*

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# 21

## Anatomy of the Male Genital Tract

Ashini Jayasuriya • Madhur Gupta

### Introduction

The male reproductive system includes the *testes*, *epididymides*, *vas deferens*, *ejaculatory ducts*, *seminal vesicles*, *prostate*, *bulbourethral glands*, and *urethra*. The urethra is a common passage for both semen and urine. The testes are suspended in the scrotal sac by the spermatic cords. The scrotum and the penis together form the *male external genitalia*.

### Testes and Epididymides

The *testes* are paired ellipsoid bodies lying within the scrotal sac that produce male sex cells called *spermatozoa*. Each testis measures approximately 4.5 cm × 3 cm × 2.5 cm in vertical, anteroposterior, and transverse diameters, respectively. The average weight of each in adults is 10–11 g. The testes are suspended in the scrotum by the *spermatic cords*. The left testis is normally about 1 cm lower than the right. Each lies obliquely within the scrotum so that the upper pole is tilted anterolaterally.

*Efferent ductules*, 12–20 in number, emerge from the upper pole of the testis. They are highly folded and tightly packed, and unite to form the *epididymis*. The epididymis occupies the upper pole and the lateral part of the posterior border of the testis as a comma-shaped mass with an enlarged head, an intermediate body, and a tapering tail (Fig. 21.1). The head of the epididymis, formed by efferent ductules, cannot be separated from the upper pole of the testis. The body and tail are, however, easily detachable from the testis as they are bounded only by loose connective tissue. The tail of epididymis ultimately forms the *ductus (vas) deferens* which ascends along the medial part of the posterior border of the testis. The epididymis is approximately 5 cm in length in its highly folded anatomical state. If unfolded, it would be about 6 m in length. Spermatozoa are carried from the testis *via* the efferent ductules to the canal of the epididymis and subsequently continue upward via the ductus deferens.

The upper pole of the testis is connected to an embryonic remnant of the paramesonephric (Mullerian) duct called the *appendix of the testis* (Fig. 21.1). This is a small, sessile, fibro-fatty body attached to upper pole just below the head of the epididymis.

The head of epididymis itself is also attached to a pedunculated body called the *appendix of the epididymis* (Fig. 21.1). This represents the degenerated cephalic part of the mesonephric (Wolffian) duct. Between the lateral surface of the testis and the medial surface of the body of epididymis lies a semilunar recess of the cavity of the tunica vaginalis called the *sinus of the epididymis*. The anterior border of the testis is free, convex and is covered by the visceral layer of the tunica vaginalis. The posterior border is flat, broad and is related to the epididymis laterally and the vas deferens medially.

Besides the extrinsic coverings contributed by the scrotum, the testis has three intrinsic coverings formed by the visceral layers of the *tunica vaginalis*, *tunica albuginea*, and *tunica vasculosa* (Fig. 21.2). The tunica vaginalis is embryologically derived from the processus vaginalis. It consists of two layers. The visceral layer, covering the testicular surface and partially covering the epididymis, is reflected off the testis at its two poles to form the parietal layer, adherent to the internal spermatic fascia. A small amount of fluid separating the two layers allows the testis to move freely in the scrotum. Internal to the visceral layer of the tunica vaginalis lays the tunica albuginea and tunica vasculosa.

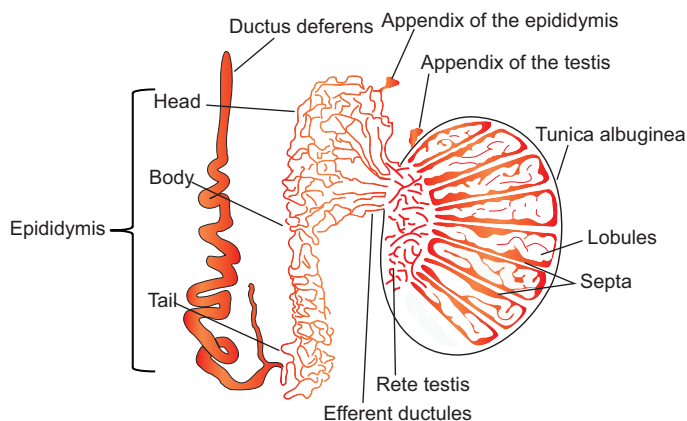
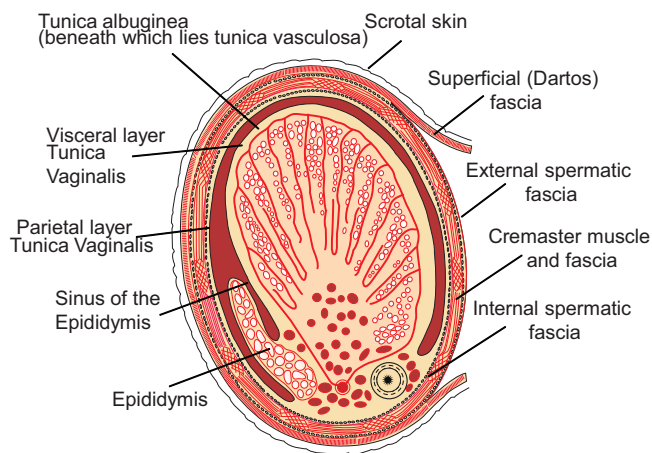


Fig. 21.1: The testis and epididymis.



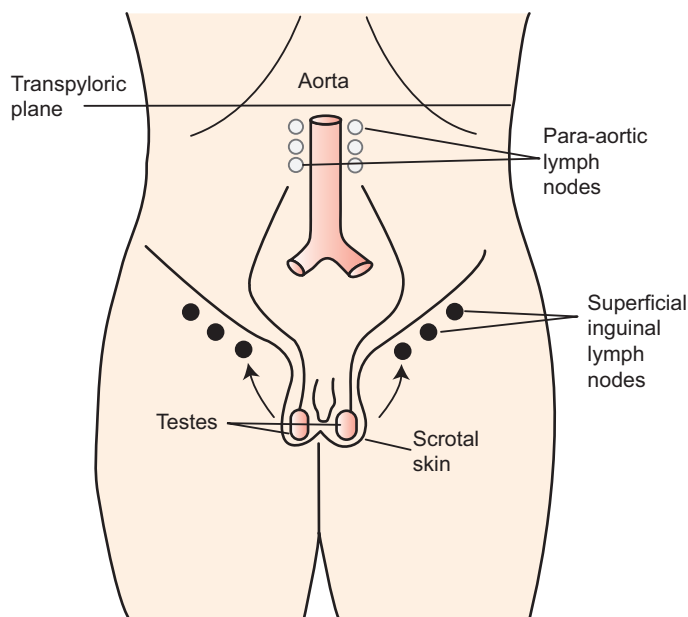
**Fig. 21.2:** Schematic drawing of a horizontal section through the scrotum.

### STRUCTURE AND FUNCTION OF THE TESTES

The visceral layer of tunica vaginalis is made up of a layer of squamous mesothelial cells resembling that of the peritoneal mesothelium. The tunica albuginea is thick, dense, fibrous, and almost avascular. It projects into the interior of the testis as an incomplete vertical partition called the mediastinum testis. Numerous septa divide the testis into 200–300 conical compartments called lobules. The tunica vasculosa is made up of a fine network of blood vessels and loose areolar tissue that lines the inner surface of the tunica albuginea and the fibrous septa that delineate each lobule. Each lobule contains 1–2 seminiferous tubules, which join to form a *rete testis* in the mediastinum. From the rete testis, 10–20 efferent ductules at the upper pole pierce the tunica albuginea and form the head of the epididymis. There are 400–500 seminiferous tubules in each testis. Each tubule, when uncoiled, is about 70–80 cm long and 0.15–0.30 mm in diameter. The coiled parts are small before puberty and are lined with two types of cells—*gonocytes* and *Sertoli cells*. A third cell type, called *interstitial (Leydig) cells*, is not prominent before puberty but increases in number thereafter. After sexual maturity, under the effect of anterior pituitary hormones, the gonocytes multiply to form spermatogenic cells. The time taken for spermatogenesis is about 64–74 days. Sertoli cells are elongated polyhedral cells extending from the basement membrane to the lumen of the tubule. They have several functions including the provision of nutrition to the immature spermatozoa, maintenance of the blood–testis barrier, phagocytosis of the residual bodies formed during spermatogenesis, and they also probably act as a source of estrogenic hormones. Leydig cells are large, polyhedral cells with an eccentric nucleus having 1–3 nucleoli and scanty, but lipid-rich, cytoplasm. They are present in the connective tissue and secrete androgenic hormones which promote development of the genitalia and accessory sex glands and male secondary sex characteristics. The hormones secreted by these cells also influence general metabolism.

### BLOOD SUPPLY, LYMPHATIC DRAINAGE, AND INNERVATION

The main arterial blood supply to the testes is provided by the *testicular artery*, a branch of the abdominal aorta, reaching the testes *via* the spermatic cords. The *artery of the vas deferens*, a branch of the inferior vesical artery, anastomoses with the testicular artery near the testis and contributes to the blood supply. The *cremasteric artery*, a branch of the inferior epigastric artery, supplies the cremaster muscle and also anastomoses with the testicular artery near the testis. About 15–20 veins emerge from the posterior border of the testis. They form the *pampiniform plexus* which surround the vas deferens and the arteries in the spermatic cord. These empty into *testicular veins* on either side. The right testicular vein drains into the inferior vena cava at an acute angle below the level of the right renal vein. The left testicular vein drains into the left renal vein almost at right angle. The veins of the pampiniform plexus act as a counter current heat exchanger to maintain the testicular temperature a few degrees below body temperature. The testes, epididymides, and spermatic cord have a rich lymphatic supply. The lymphatics run along the testicular artery to para-aortic nodes situated adjacent to the inferior vena cava and aorta below the renal veins (Fig. 21.3). Testicular tumors metastasize to these nodes. Both testes and epididymides are supplied by sympathetic fibers from the aortic and renal plexuses via branches passing along the testicular vessels and artery of the vas deferens. Preganglionic sympathetic fibers to the testis are derived from T10 to T12 spinal segments, thus pain of testicular origin is referred to the umbilical region and lower abdominal wall. The tunica vaginalis of the testis is supplied by the genitofemoral nerve (L1–L2).



**Fig. 21.3:** Lymphatic drainage of the testes and the scrotal skin.



## APPLIED ANATOMY

The testes develop in the lumbar region and pass through the inguinal canal into the scrotum just before birth. Maldescent of a testis (*cryptorchidism*) is seen in about 3% of full-term and 30% of premature infants. Most undescended testes will descend within a few weeks of birth. Normal spermatogenesis does not occur in the undescended testes. As changes occur early, orchidopexy (surgical procedure to bring down the testis) is best performed at about 6–12 months, but certainly before 2 years of age. Malignant changes occur much more frequently in undescended testes.

Testicular tumors, although relatively rare, are one of the most common malignant tumors of young adults with a peak incidence in men aged 25–40 years (and a second peak in those over 60 years). Over 90% of testicular tumors are now curable with multimodal therapy.

*Varicoceles* (varicose veins of the spermatic cord) are nearly always left-sided and arise when the pampiniform plexus of veins is distended owing to incompetence of the valves of the testicular vein. On palpation, they are described as feeling like a ‘bag of worms.’ This swelling, best felt with the patient standing, usually disappears when the patient lies down and the scrotum is elevated. Varicoceles are generally seen in young men. Onset in older men may be associated with a renal tumor spreading to the left renal vein and consequent obstruction of the testicular vein. Right-sided varicosities may be associated with situs inversus or anomalous drainage of the testicular vein into right renal vein.

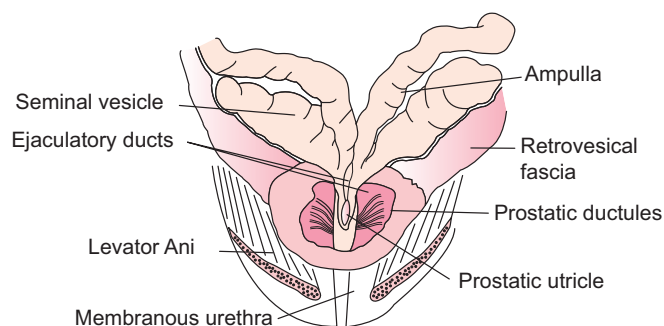
The testis can rotate around the spermatic cord within the scrotum. Torsion of the testis is often associated with a large tunica vaginalis. Torsion commonly occurs in young men and children and is accompanied by severe pain. If treatment is delayed, the arterial supply may be occluded followed by death and necrosis of testicular tissue. The testicular appendix may also undergo torsion causing acute testicular pain that may be mistaken for a testicular torsion.

## SPERMATIC CORD

Spermatic cords suspend each testis in the scrotum. Each begins at the deep inguinal ring, passes through the inguinal canal, emerges through the superficial inguinal ring and descends in the scrotum to end at the posterior border of the testis. Within the coverings of the cord are the ductus (vas) deferens, the testicular artery, the artery of the ductus deferens, the cremasteric artery, the pampiniform plexus of veins, autonomic sensory nerves, and the genital branch of the genitofemoral nerve. Lymphatic vessels draining the testes are also found within the spermatic cord.

## Ductus Deferens

The *ductus deferens* transports spermatozoa from the testis to the prostatic urethra. It is approximately 45 cm long and has a thick muscular wall with a narrow lumen. It commences as a continuation of the tail of the epididymis and ascends along the posteromedial side of the testis and through the inguinal



**Fig. 21.4:** Section through the prostate gland, demonstrating the passage of the ductus deferens and its connections within the prostate.

canal as a part of the spermatic cord. At the bladder base, it passes medial to the seminal vesicle. It then dilates to form the *ampulla of the ductus deferens*. It joins the duct of the seminal vesicle at an acute angle to form the *ejaculatory duct*, which passes through the parenchyma of the prostate and opens on either side of the prostatic utricle on the *colliculus seminalis* of the prostatic urethra (Fig. 21.4).

## STRUCTURE AND FUNCTION

The wall of the ductus deferens consists of four layers; (from outside inward) the *adventitia*, the *muscular layer*, the *lamina propria*, and the *epithelium*. The epithelium consists of pseudostratified columnar cells with long regular microvilli (stereocilia). The cells are considered to have some secretory functions, especially in the abdominal and prostatic segments. The muscle coat is made up of three layers: inner and outer longitudinal and in between, circular smooth muscle. The contractions of the muscular wall transport of spermatozoa to the prostatic urethra.

## BLOOD SUPPLY AND INNERVATION

The ductus deferens has its own artery, usually derived from the superior vesical artery which anastomoses with the testicular artery. The venous drainage is supplied by corresponding arteries. The nerves of the ductus deferens are derived from the inferior hypogastric plexus. It has a rich innervation of sympathetic nerve fibers, which enable rapid contraction and expulsion of sperm during ejaculation.

## APPLIED ANATOMY

Bilateral *vasectomy* is performed under local anesthesia as a permanent method of contraception by dividing the vas deferens between ligatures. Spermatozoa may be present in the first few postoperative ejaculations. Afterwards, only the secretions of the seminal vesicles and prostate constitute the ejaculated seminal fluid. Vasectomy is an effective form of contraception with a low failure rate of 1:2000.

## Seminal Vesicles

Seminal vesicles are paired accessory sex glands, approximately 5 cm in length, embedded in connective tissue on the posterior surface of bladder. When uncoiled, each is 10–15 cm in length. The wider, blind end of the vesicle lies behind the ureter and joins the vas deferens just above the base of the prostate by means of its ejaculatory duct. These begin just above the base of the prostate, are about 2 cm long, and lie almost completely within the prostate. They course obliquely forward, medially, and downward to converge at the prostatic urethra where they open at the *colliculus seminalis* (Fig. 21.4). The seminal vesicles drain the seminal fluid into the prostatic urethra.

### STRUCTURE AND FUNCTION

The seminal vesicles have an external connective tissue coat (adventitia), a thin muscle coat, and an inner mucous coat. The muscle coat has outer longitudinal and inner circular layers of smooth muscle fibers. The mucosal layer is made of simple columnar secretory epithelium with apical microvilli. It is thrown into many folds. Some goblet and stem cells are also present. The seminal vesicles are mainly secretory in function and their secretory products make up 70% of the seminal fluid. These products include potassium ions, fructose, prostaglandin, endorphin, fibronectin, carbonic anhydrase, transferrin, and sperm motility factors. These are concerned with the modification of the motility of sperm. These products also make the semen alkaline. The walls of the seminal vesicles contract during ejaculation and expel their contents into the ejaculatory ducts.

### BLOOD SUPPLY AND INNERVATIONS

The arterial supply of the seminal vesicles is from the inferior vesical and middle rectal arteries. Draining veins follow the arteries. The nerve supply to the seminal vesicles is from the hypogastric autonomic plexus. The secretory activity is regulated primarily by cholinergic fibers from the pelvic splanchnic nerves and testosterone.

### APPLIED ANATOMY

When swollen or inflamed, the seminal vesicles become tender on palpation during rectal examination. An abscess here may rupture into the peritoneal cavity. The seminal vesicles contract a little earlier than the vas deferens during sympathetic stimulation for ejaculation. Hence, the first part of the ejaculate is mainly the secretion from the seminal vesicles with few spermatozoa.

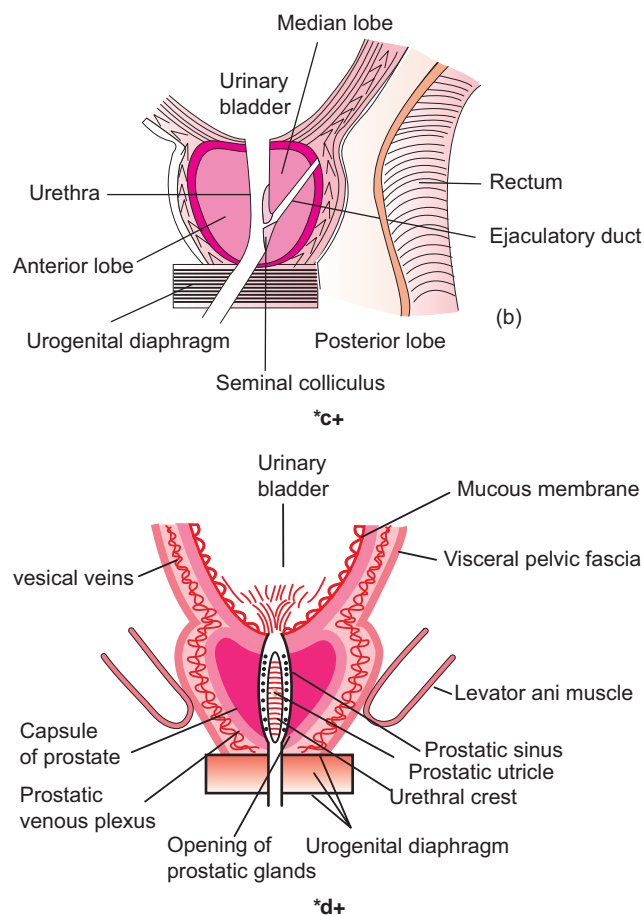
## Prostate

The prostate gland is composed of glandular and fibromuscular tissue surrounded by a thin dense fibrous capsule (true capsule) and an outer, loose sheath of pelvic fascia (false capsule). It is traversed by the urethra and comprises apex, base, anterior, posterior, and two inferolateral surfaces. The prostate is approximately 4 cm

in transverse diameter at the base, 3 cm in vertical diameter, 2 cm anteroposteriorly, and usually weighs about 8 g. The apex is directed downward and lies on the upper surface of the urogenital diaphragm. The base is directed upward and is closely related to the neck of the bladder. The urethra enters the gland by piercing the base in the midline at the junction of its anterior one-third and posterior two-thirds. It passes vertically downward from the base to the apex, and exits the gland through its anterior surface just above and in front of the apex (Fig. 21.5 a and b).

The prostate is divisible into lobes. The two lateral lobes are separated posteriorly by a shallow median groove. Because these lobes are often fused, they are sometimes known as the posterior lobe. Superiorly on the posterior surface, a transverse groove between the entry points of the two ejaculatory ducts represents the median lobe of the prostate. The anterior lobe is the fibromuscular isthmus joining the two lateral lobes in front of the urethra (Fig. 21.5a).

Two ejaculatory ducts pass posterolaterally to the median lobe and open at the colliculus seminalis. A diverticulum from this part of the prostatic urethra, the prostatic utricle, extends upward and backward for about 6 mm from the centre of the colliculus seminalis (Fig. 21.5b).



**Fig. 21.5:** (a) Sagittal section through the prostate gland. (b) Coronal section through the prostate gland demonstrating the structures within the gland.

## STRUCTURE AND FUNCTION

The moderately thick stromal connective tissue, forming the true capsule, surrounds and supports the glandular element of the prostate. A condensation of endopelvic fascia forms the false capsule. It blends anteriorly with the puboprostatic ligaments. Below, it blends with the superior layer of the urogenital diaphragm and the perineal body. Posteriorly the false capsule blends with the rectovesical fascia of Denonvilliers. The space between the true and false capsules contains the prostatic venous plexus (Fig. 21.5a).

About a quarter of the prostatic mass is muscle tissue, another quarter is connective tissue, and remaining half is secretory glandular tissue. The glandular elements are composed of secretory follicles lined by simple columnar epithelium. The glands are embedded in the fibromuscular part and are arranged more or less concentrically in three layers around the urethra. The mucosal glands in the periurethral tissue are the smallest, open at various points around the lumen of the urethra, and may form adenomatous nodules (usually in older age). The second layer is that of submucosal glands. The external, 'true' prostatic glands have tubuloalveolar secretory units and are located in the outermost part of the gland. The normal glandular activity of the prostate is controlled by androgens. Prostatic secretion, a thin, milky fluid, is discharged into the prostatic urethra by contraction of smooth muscle in the prostate. Prostatic secretions provide approximately 20% of the volume of seminal fluid and contain citric acid and acid phosphatase.

## BLOOD SUPPLY, LYMPHATIC DRAINAGE, AND NERVE SUPPLY

Branches from the *inferior vesical*, *middle rectal*, and *internal pudendal arteries* supply the prostate. The veins draining the gland form a plexus in the space between true and false capsules. This venous plexus receives the *deep dorsal vein of the penis* and communicates with the *vesical venous plexus*. From this plexus, veins pass along the posterior ligament of the bladder into the internal iliac veins. The prostatic venous plexus also communicates with the extradural internal vertebral venous plexus through the anterior sacral foramina. During coughing and sneezing or abdominal straining, it is possible for prostatic venous blood to flow in a reverse direction and enter the vertebral veins. This explains the frequent occurrence of skeletal metastasis in the lower vertebral column and pelvic bones of patients with carcinoma of the prostate. Cancer cells enter the skull via this route by floating up the valveless prostatic and vertebral veins. Lymphatic vessels from the prostate pass mainly to the internal iliac and sacral lymph nodes. A few lymphatics may drain into the external iliac lymph nodes. The prostate is richly supplied with sympathetic and parasympathetic nerve fibers. The former are derived from the inferior hypogastric plexus and the latter from the pelvic splanchnic nerves (S 2, 3, and 4). Pain due to prostatitis hence tends to be referred to the perineum.

## APPLIED ANATOMY

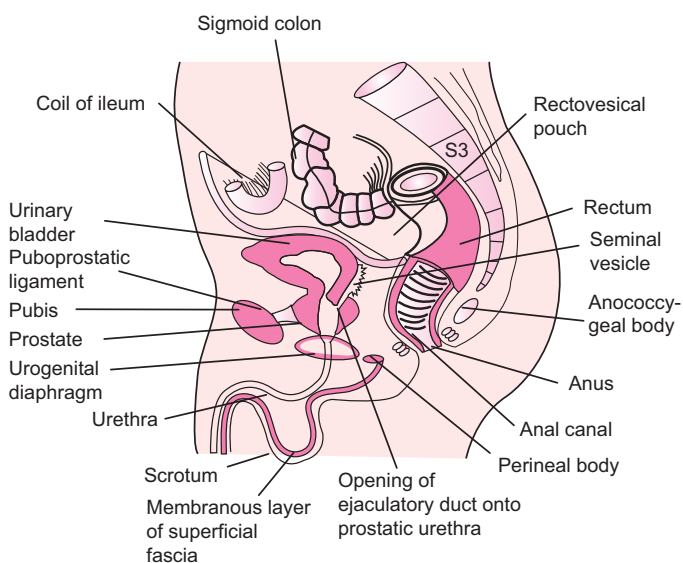
The prostate can be examined clinically by performing a *digital rectal examination*. The examiner's gloved index finger is placed in the anal canal and rectum. This allows for the posterior surface of the prostate to be felt through the anterior rectal wall. The following structures can also be palpated by this examination. Anteriorly, opposite the terminal phalanx are the contents of the rectovesical pouch, the posterior surface of the bladder, the seminal vesicles, and the vas deferens. Opposite the middle phalanx are the rectoprostatic fascia and the prostate, and opposite the proximal phalanx are the perineal body, the urogenital diaphragm, and the bulb of the penis (Fig. 21.6).

Trace amounts of proteins produced specially by prostatic epithelial cells are found in the peripheral blood. In certain prostatic diseases, notably cancer of the prostate, this protein appears in the blood in increased amounts. The *prostatic specific antigen* test measures these protein levels.

In prostatic operations, the prostatic venous plexus poses a risk of severe hemorrhage, being thin-walled, valveless, and draining directly into larger internal iliac veins.

*Benign hyperplasia* of the prostate is common in older men, particularly after the age of 50. The median lobe of the gland enlarges upward and encroaches on the sphincter vesicae at the neck of the bladder. The leakage of urine into the prostatic urethra causes an intense reflex desire to micturate. The enlargement of the median and lateral lobes of the gland produces elongation and lateral compression and distortion of the urethra (ball-valve effect) so that the patient experiences difficulty in passing urine and the stream is weak. The enlargement of uvula vesicae due to an enlarged median lobe results in the formation of a pouch of stagnant urine within the bladder which may become infected.

Owing to the relationship of the prostate to the prostatic urethra, urethral obstruction may be relieved by a *transurethral*



**Fig. 21.6:** Sagittal section demonstrating the anatomical relationship of the male pelvis.



*resection of the prostate.* Partial or complete removal of the prostate is called *prostatectomy*.

## Scrotum

The scrotum is an outpouching of the lower part of anterior abdominal wall and contains the testes, epididymides, and lower part of the spermatic cord. It develops embryologically from two outpouchings of the anterior abdominal wall called *labioscrotal swellings* which fuse in the midline. The *median subcutaneous raphe* divides the scrotum into the right and the left halves.

The wall of scrotum has the following layers from outside inward: the skin, the dartos muscle continuous with the superficial fascia (Colles') of the perineum, external spermatic fascia derived from the external oblique muscle, the cremasteric fascia derived from the internal oblique muscle, and the cremaster muscle. Internal to this lies the internal spermatic fascia derived from the fascia transversalis and the parietal layer of tunica vaginalis (Fig. 21.2).

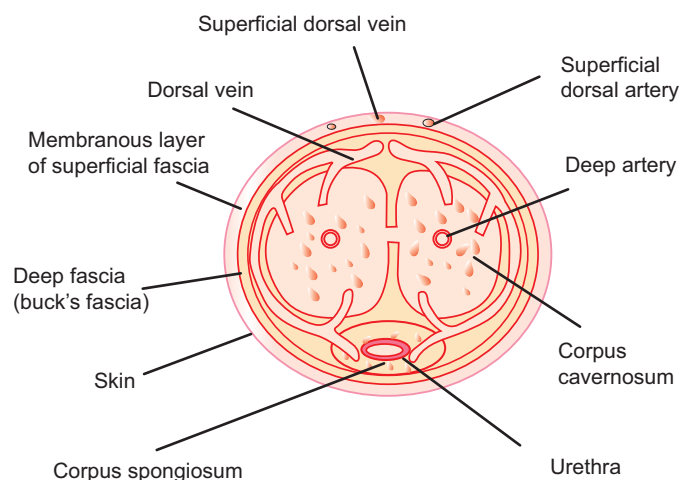
Scrotal skin is darker and rugose. It contains numerous sebaceous and sweat glands with scattered coarse hairs that appear after puberty. The evaporation of sweat helps to lower the scrotal temperature. The skin, being adherent to the underlying dartos muscle, becomes corrugated when this muscle contracts, especially in children, young adults, and in cold temperature. There is no subcutaneous adipose tissue in the scrotum. Edema, secondary to cardiac or renal failure, tends to collect within the scrotum, as it is a suspended organ and the skin is lax and stretches easily.

## BLOOD SUPPLY, LYMPHATIC DRAINAGE, AND INNERVATION

The scrotum is supplied by perineal branches of the internal pudendal arteries, the superficial and deep external pudendal branches of the femoral artery, and the cremasteric branch of inferior epigastric artery. The scrotal veins accompany the arteries and drain partly into the internal iliac and partly into the great saphenous vein. Arteriovenous anastomoses promote heat loss, thus assist in the control of the temperature of the testis which is important for spermatogenesis. Lymph vessels from the wall of the scrotum drain into the medial group of superficial inguinal lymph nodes (Fig. 21.3). Sensory supply to the anterior third of the scrotum is from the L1 spinal segment via the genitofemoral and ilioinguinal nerve. The genitofemoral nerve also supplies to the cremaster muscle. The sensory supply to the posterior two-thirds is from S3 and S4 spinal segments via the posterior scrotal branches of pudendal nerve and the perineal branch of the posterior cutaneous nerve of the thigh (posteroinferior scrotum). The dartos muscle is supplied by sympathetic nerves from the superior hypogastric plexus.

## Penis

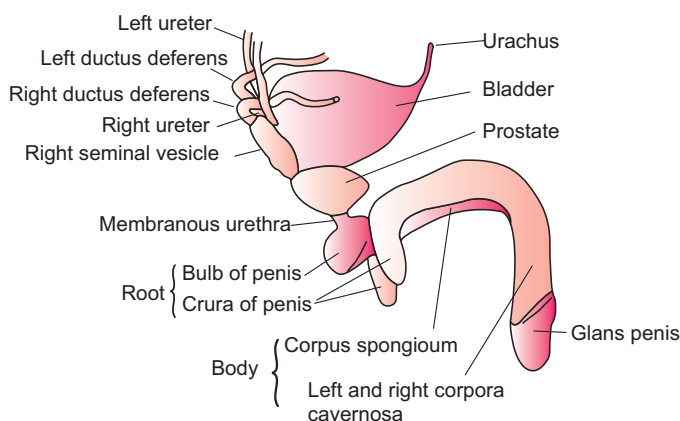
The penis is the male organ of copulation and the outlet for semen and urine in a male. It consists of three parallel, cylindrical



**Fig. 21.7:** Cross-section through the penis demonstrating erectile tissue and blood supply

bodies of erectile tissue enclosed in a fibrous capsule called the tunica albuginea (Fig. 21.7). Superficial to this is a tubular sheath of fascia called the deep fascia of the penis (Buck's fascia). The two dorsally placed *corpora cavernosa* are attached to the sides of the pubic arch. They diverge in the perineum to form the *crura* of the penis but are fused together in the body of the penis. The *corpus spongiosum* lies on the ventral (urethral) surface between the corpora cavernosa and transmits the urethra. Proximally, it is enlarged to form the *bulb* of the penis and is attached between the crura to the inferior layer of the urogenital diaphragm. Distally, it expands to form the glans penis into which the tapered ends of the corpora cavernosa are inserted (Fig. 21.8).

The urethra traverses the glans and opens through as a vertical slit, the *external urethral orifice*. The glans penis is conical in shape. The margin of its base projects outward and is called the corona of the glans. The glans has a higher concentration of sensory nerve endings than the rest of the body of the penis. The cavernous erectile tissue of which the corpora are composed consists of intercommunicating spaces which are separated by fibrous trabeculae and are filled with blood during penile erection.



**Fig. 21.8:** The male penis.



The skin of the penis is delicate, elastic, and hairless except at the base. It is freely movable over the surface and distally forms a free fold (or double layer) called the *prepuce*, which extends over the glans for a variable distance and allows for the collection of secretions of the preputial glands called smegma. In the midline, a narrow, free fold of skin (the *frenulum of the prepuce*) passes from the urethral surface to the deep aspect of the prepuce.

The superficial fascia of the penis is composed of loose areolar tissue without fat. The deep fascia forms a close fitting sheath around the corpora. The penis is supported by the fundiform ligament and the suspensory ligament. The latter is a fibroelastic structure, which spreads out from the anterior surface of the pubic symphysis to fuse with the deep fascia on the dorsum and sides of the penis. The dorsal vessels and nerves lie deep to it. The fundiform ligament arises from the membranous layer of the subcutaneous tissue of the lower abdomen.

### BLOOD SUPPLY, LYMPHATIC DRAINAGE, AND NERVE SUPPLY

The arterial supply to the corpora is provided by the *deep arteries of the penis*. The corpus spongiosum is also supplied by the *artery of the bulb*. The skin of the organ is supplied by the *dorsal artery of the penis*. All the above arteries are branches of the internal pudendal arteries which themselves arise from the internal iliac arteries (Fig. 21.9). The deep arteries are the principal supply to the cavernous spaces in the three corpora during erection. They give off numerous branches which open directly into the

cavernous spaces, called *helicine* arteries. The venous drainage from the cavernous spaces is by means of a venous plexus which joins the deep dorsal vein located in the deep fascia. This in turn drains into the prostatic plexus of veins by passing below the symphysis pubis. The superficial coverings of the penis drain into the superficial dorsal vein which lies in the superficial fascia. It divides proximally into right and left branches, which pass into the external pudendal veins. The lymphatic drainage of the penile skin is into the medial group of superficial inguinal nodes. The deep structures drain into the internal iliac nodes. The lymphatic drainage of the glans is directly into deep inguinal nodes. The innervation of the penis is supplied by the pudendal nerve via the dorsal nerve of the penis and autonomic nerves from the inferior hypogastric plexus. The skin covering the root of the penis is supplied by the ilioinguinal nerve, the perineal branches of the posterior cutaneous nerve of the thigh, and the posterior scrotal branches of the perineal nerve.

### APPLIED ANATOMY

Following erotic stimulation, smooth muscle in the fibrous trabeculae and the walls of the helicine arteries undergo relaxation due to parasympathetic stimulation. As a result these arteries, which are coiled in the flaccid state, straighten and their lumina enlarge allowing blood to flow into the cavernous spaces. The bulbospongiosus and ischiocavernosus muscles compress the venous plexuses at the periphery of the corpus cavernosa, to prevent venous return. The corpora therefore enlarge and the penis becomes erect. Detumescence takes place post ejaculation, where secondary to sympathetic stimulation, smooth muscle in the helicine arteries constrict, and the bulbospongiosus and ischiocavernosus muscles relax, allowing the cavernous spaces to empty and the penis to return to the flaccid state.

*Circumcision* is the surgical removal of the prepuce. This may be done for religious or hygiene reasons. There is now accumulating evidence that circumcised individuals may be less susceptible to certain types of viral sexually transmitted infections including HIV and HPV as compared to their uncircumcised counterparts.

### Male Urethra

The male urethra is about 20 cm long and extends from the neck of the bladder to the external meatus on the glans penis. It is divided into three parts, namely, *prostatic*, *membranous*, and *penile*.

The prostatic urethra is 3 cm long. It passes from the internal urethral orifice at the apex of the trigone of the bladder through the prostate, to reach the urogenital diaphragm, at which point it continues as the membranous urethra. It is the widest and most distensible portion of the urethra. On the posterior wall is a longitudinal ridge called the urethral crest or *verumontanum*. On either side of this ridge, there is a groove called the prostatic sinus into which the prostatic glands open. On the summit of the urethral crest is a depression, the prostatic utricle, which is

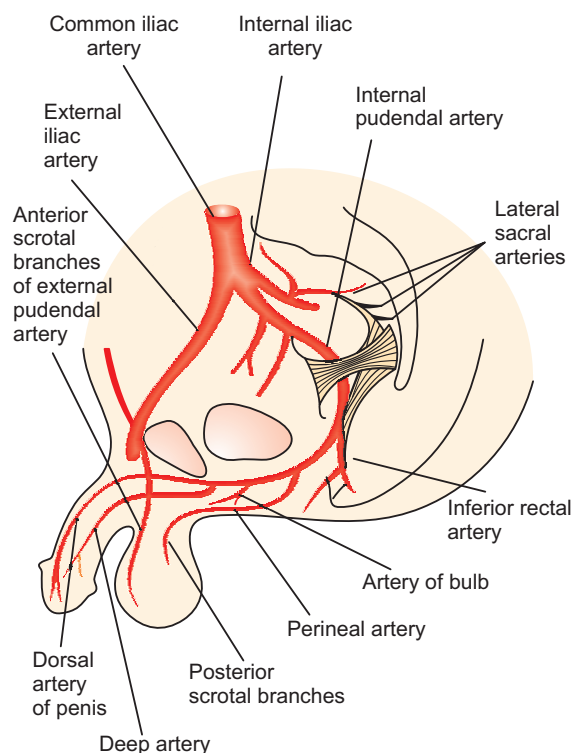
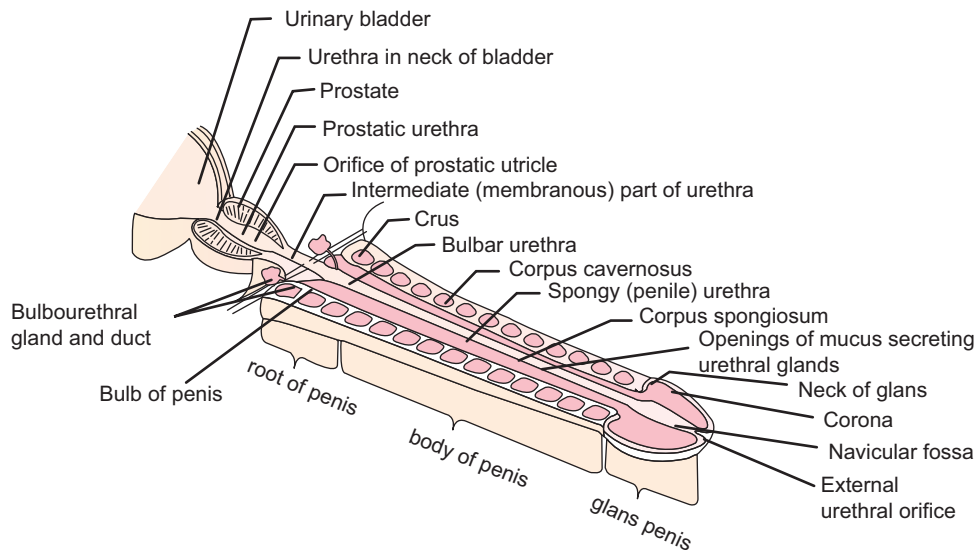


Fig. 21.9: Arterial supply of the male external genitalia.



**Fig. 21.10:** The longitudinal section of the penis to demonstrate the urethra and associated structures by schematic diagram.

analogous to the uterus and vagina in the female. On the edge of the mouth of the utricle are the openings of the two ejaculatory ducts (Fig. 21.10).

The membranous urethra is about 1–2 cm long and lies within the urogenital diaphragm surrounded by the sphincter urethrae muscle. Distally, it is continuous with the penile urethra. It is the shortest and least dilatable portion of the urethra (Fig. 21.10). The sphincter urethrae surround the urethra in the deep perineal pouch. It arises from the right and left pubic arch and passes medially on the posterior surface to encircle the urethra. It is supplied by the perineal branch of the pudendal nerve. The muscular sphincter which compresses the membranous part of the urethra relaxes during micturition. Contraction of this muscle allows for micturition to be voluntarily stopped.

The penile urethra is about 15 cm long and is enclosed in the bulb and the corpus spongiosum of the penis. The bulbourethral glands open into the penile urethra below the urogenital diaphragm. Within the bulb, the urethra is dilated to form the intrabulbar fossa and within the glans, to form the navicular fossa. The penile urethra ends at the external urethral meatus. This is the narrowest part of the entire urethra (Fig. 21.10).

### Bulbourethral Glands

The two bulbourethral glands are yellowish, rounded, pea-sized, glandular masses within the deep perineal pouch. They lie on either side of the membranous urethra, above the perineal membrane and bulb of the penis in the deep perineal pouch and are enclosed by fibers of the sphincter urethrae. They gradually diminish in size in older age. The duct of each gland passes obliquely forward through the perineal membrane, and empties secretions into the penile urethra about 2.5 cm below the perineal membrane. The bulbourethral glands contain tubuloalveolar cells producing mucoid substances. These secretions have been shown to contain a

number of enzymes including  $17\beta$  hydroxysteroid dehydrogenase. Nerve fibers sensitive to vasoactive intestinal polypeptide have been observed around the secretory units. Diffuse lymphoid tissue and intraepithelial lymphocytes, monocytes, and macrophages are also present in these glands which help in combating infections. Secretions are poured into the urethra during the parasympathetic stimulation associated with erection.

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# 22

## Anatomy of the Female Genital Tract

Ashini Jayasuriya • Madhur Gupta

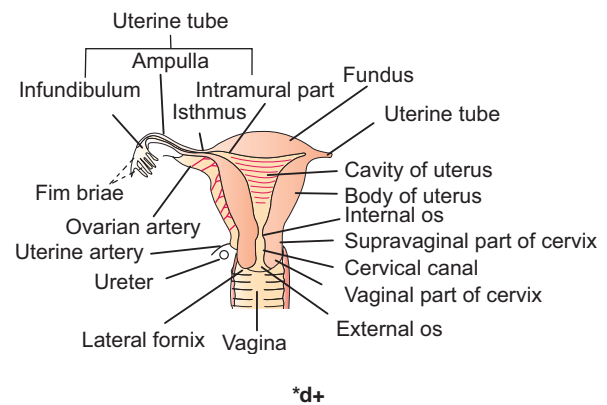
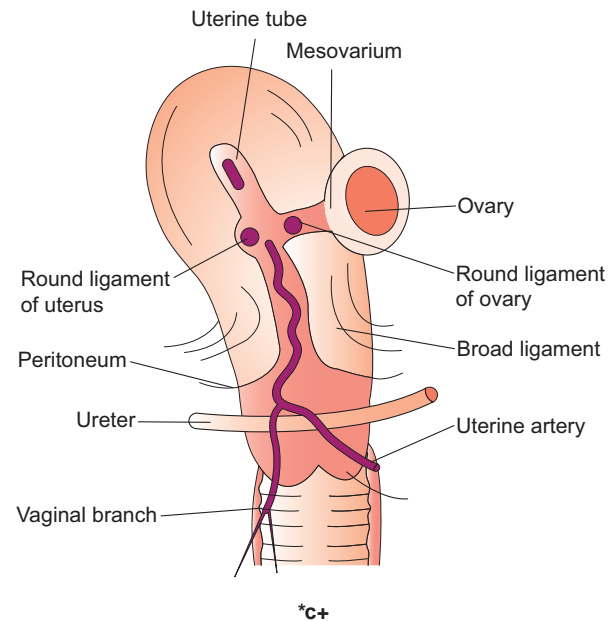
### Introduction

The female *genitalia* or genital organs consist of internal and external structures. The internal genitalia, situated within the lesser pelvis, are the ovaries, uterine tubes, uterus, and vagina. The external genitalia lying in front and below the pubic arch are the mons pubis, labia majora, labia minora, pudenda, clitoris, bulb of the vestibule, and greater vestibular glands.

### Ovaries

Ovaries are paired, almond-shaped organs homologous to the testes in men. In nulliparae, the ovaries are pinkish white structures, measuring 2–4 cm in length, 1.5 cm in width, and 1 cm in thickness. Each ovary is attached to the posterior surface of the *broad ligament* by a peritoneal fold called the *mesovarium* (Fig. 22.1a). The part of the broad ligament extending between the attachment of the mesovarium and the lateral wall of the pelvis is called the *suspensory ligament* of the ovary. The ovary is connected to the lateral margin of the uterus by the *round ligament of the ovary* or *ovarian ligament*.

The ovary usually lies against the lateral wall of the pelvis in a depression called the *ovarian fossa*, bounded above by the external iliac vessels, in front by the obliterated umbilical artery, and behind by the ureter and internal iliac vessels. The peritoneum of the floor of the fossa separates the ovary from the underlying obturator nerve and vessels. The surface of the ovary is not covered by the peritoneum, hence during ovulation the oocyte is expelled into the peritoneal cavity. The oocyte is then trapped by the *fimbriae* of the *uterine tube* and carried to the ampulla. The ovary is kept in position by the broad ligament and mesovarium. After pregnancy, the broad ligament may become lax and the ovary may prolapse into the rectouterine pouch (pouch of Douglas). In these circumstances, the ovary may be tender and cause discomfort on sexual intercourse (*dyspareunia*). An ovary situated in the rectouterine pouch may be palpated through the posterior fornix of the vagina.



**Fig. 22.1:** (a) Lateral view of the uterus and ovary, demonstrating the structures which lie within the broad ligament. (b) Structure of the uterus and uterine tubes.

## BLOOD SUPPLY, LYMPHATIC DRAINAGE, AND INNERVATION

The *ovarian arteries* arise from the abdominal aorta at around the first/second lumbar vertebrae and reach the ovaries after descending along the posterior abdominal wall, crossing the external iliac vessels at the pelvic brim and passing through the ovarian suspensory ligaments. Before anastomosing with the *uterine artery*, a branch of each ovarian artery passes through the mesovarium to supply its respective ovary. The right *ovarian vein* drains into the inferior vena cava at an acute angle. The left ovarian vein drains into the left renal vein almost at a right angle. Lymphatic vessels follow the ovarian vessels and drain into *pre-aortic* and *para-aortic lymph nodes*. Nerve fibers descend along the ovarian vessels from the ovarian plexus that communicates with the uterine plexus. Sympathetic preganglionic fibers are derived from T10–T11 segments of the spinal cord. Parasympathetic fibers are derived from the *vagus nerve*. Afferent fibers from the ovaries reach the central nervous system from the dorsal route of the T10 spinal nerve.

## FUNCTIONS

The ovaries have two interrelated functions: the production of *gametes (oogenesis)* and the production of *steroids (steroidogenesis)*. Developing gametes are called oocytes, and post-ovulation, are called ova. The major groups of steroid hormones secreted by the ovaries are *estrogens* and *progestogens*. The estrogens promote growth and maturation of internal and external sex organs and are responsible for the typical female characteristics that develop at the time of puberty. They also act on the mammary glands to promote breast development, by stimulating ductal and stromal growth and the accumulation of adipose tissue. The progestogens prepare the internal sex organs, mainly the uterus, for pregnancy by promoting secretory changes in the endometrium. They also promote lobular proliferation of mammary glands for lactation. Both groups of hormones play an important role in the regulation of the menstrual cycle by preparing the uterus for implantation of the fertilized ovum. If implantation does not occur, the uterine endometrium undergoes degeneration and is shed as menstruation.

## APPLIED ANATOMY

Inflammation of an ovary may produce localized peritonitis of the ovarian fossa and irritation of the obturator nerve.

At ovulation, some women experience paraumbilical pain called '*mittelschmerz*' due to pain referred to the T10 dermatome.

On the right hand side, the vermiform appendix in some women lies close to the ovary and uterine tube. A ruptured tubal ectopic pregnancy may therefore be misdiagnosed as acute appendicitis.

Follicular cysts are common and originate from unruptured graafian follicles. They rarely exceed 1.5 cm in diameter. Luteal cysts are formed in the corpus luteum due to fluid retention preventing the corpus luteum from becoming fibrosed. Luteal cysts rarely exceed 3 cm in diameter.

Polycystic ovarian disease (Stein–Leventhal syndrome) is characterized by bilateral enlarged polycystic ovaries. Although the pathogenesis is not clear, it may be caused by abnormal levels of different steroid hormones.

A wide mesovarium and long suspensory ligament predispose to torsion of the ovary. Torsion is a complication in 10–20% of cases of ovarian tumor.

## Uterus

The uterus in a non-pregnant woman is shaped like inverted pear and is a thick walled, hollow, muscular organ. It is normally situated in the lesser pelvis between the urinary bladder and the rectum. On average, the uterus is 7–8 cm long, 5–7 cm wide, and 2–3 cm thick. The uterus consists of two major parts: an upper muscular part, the *body*, and a lower fibrous part, the *cervix*. Between these two lies the *isthmus*, a slightly constricted fibromuscular region corresponding to the *internal ostium* (Fig. 22.1b). Before puberty the uterine body and the cervix are approximately equal in length, but in adulthood the body enlarges to a ratio of 2:1 or 3:1. The rounded upper part of the body that lies above the entrance of uterine tubes at the cornu of the uterus is known as the *fundus* of the uterus.

The cervix is about 2.5 cm long and for descriptive purposes, can be divided into a *supravaginal* and a *vaginal* part. The vaginal part projects through the anterior wall of the upper part of the vagina, communicating with the vagina through the *external ostium* of the uterus. This opening is small and rounded in the nulliparous state, but in multipara may resemble a transverse slit, thus producing an anterior and a posterior cervical lip. The supravaginal part of the cervix, which expands greatly in pregnancy after about 24 weeks of gestation, forms the lower uterine segment, through which cesarean section can be performed. The supravaginal part of the cervix is surrounded by visceral pelvic fascia, often referred to as the *parametrium*. It is in this fascia that the uterine artery crosses the ureter on each side of the cervix.

The uterus normally projects superioanteriorly over the urinary bladder, i.e. bending forward at a right angle to the vagina—*anteversion*—and bending forward on the cervix—*anteflexion*. In 20% of individuals, the uterus is bent backward relative to the vagina—*retroversion*. If also bent backward, it is additionally described as being *retroflexed* (Fig. 22.2).

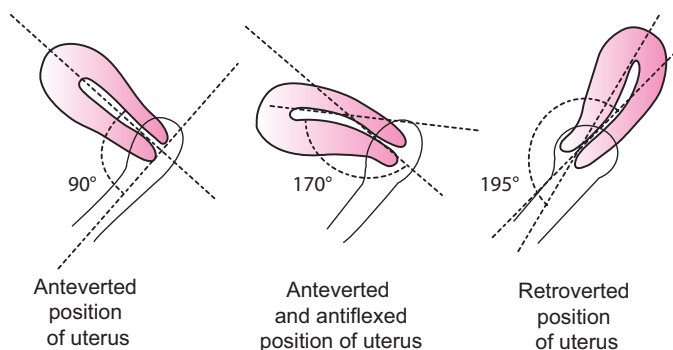
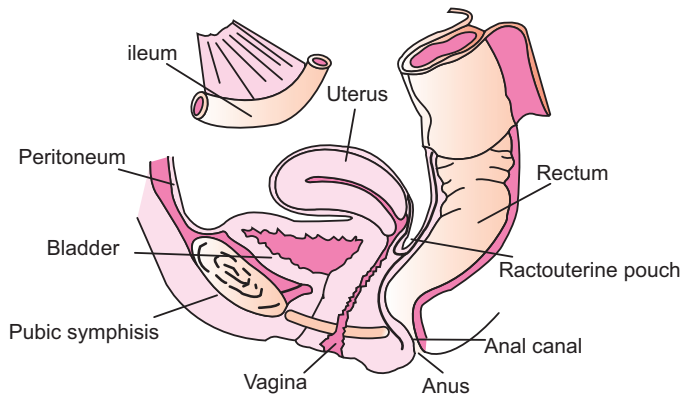


Fig. 22.2: Common positions of the uterus.





**Fig. 22.3:** Anatomical relationships within the female pelvis.

In the anteverted and anteflexed position, the body of the uterus is related anteriorly to the *vesicouterine pouch* and the superior surface of the urinary bladder. Here the peritoneum is reflected from the uterus onto the posterior surface of the bladder. As the ureters pass forward to enter the bladder, they lie in proximity to the supravaginal cervix. The body of the uterus is related posteriorly to the *rectouterine pouch* (*pouch of Douglas*) which separates it from the sigmoid colon. The inferior part of this pouch is closely related to the posterior vaginal fornix (Fig. 22.3). Lateral to the body of the uterus lie the broad ligament and the uterine vessels. The round ligament of the uterus is attached just behind the entrance of the uterine tube into the cornu of the uterus. The broad ligaments are two-layered folds of the peritoneum that extend across the pelvic cavity from the lateral margins of the uterus to the lateral pelvic walls.

### BLOOD SUPPLY, LYMPHATIC DRAINAGE, AND INNERVATION

The *uterine arteries* are branches of the internal iliac arteries. They run downward, forward, and medially across the levator ani muscle and then, at the base of the broad ligament, cross anterior to and above the ureters, about 2 cm lateral to the vaginal fornix. Having crossed over the ureter, each uterine artery passes upward along the lateral margin of the uterus, between the two layers of the broad ligament, supplying the uterus and uterine tube and anastomosing with the ovarian artery. At the isthmus, each gives off a descending branch that supplies the cervix and vagina. Part of the blood supply to the uterus is also supplied by the *ovarian arteries*, arising from the abdominal aorta (Fig. 22.1b). The *uterine veins* enter the broad ligaments alongside their arterial counterparts and form a *uterine venous plexus* on either side of the cervix which subsequently drains into the internal iliac veins. The uterine venous plexus is also connected to the superior rectal vein, forming a *portal-systemic anastomosis*. The majority of lymphatic vessels from the fundus of the uterus drain into the *pre- and para-aortic* group of lymph nodes. A few lymph vessels from the lateral angles run along the round ligament to drain into the medial group of the *superficial inguinal lymph nodes*. Lymphatic vessels from the upper parts of the uterine body enter the *external iliac lymph nodes* and lymphatics along the lower uterine body and

the cervix enter the *internal iliac and sacral lymph nodes*. There is also a *paracervical lymph node* along the side of the cervix in the connective tissue which may be the first node to be involved in the spread of cancer of the cervix. The uterus is richly supplied by sympathetic (T12–L1) and parasympathetic nerves (S2–4) through the inferior hypogastric and ovarian plexuses. Sympathetic innervation results in uterine contraction and vasoconstriction. The parasympathetic nerves inhibit uterine contractions and lead to vasodilatation. These effects are, however, complicated by the pronounced effects of hormones on the genital tract.

Painful stimuli from the uterine body pass through the sympathetic nerves to the spinal cord and presacral neurectomy may relieve pain in cases of spasmodic dysmenorrhea, not relieved by other means. Pain sensations from the cervix and upper vagina are conveyed predominantly *via* the parasympathetic nerves to S2–4 spinal segments.

### UTERINE SUPPORTS AND LIGAMENTS

The uterus is maintained in position by condensations of the pelvic fascia known as the *transverse cervical ligaments*, the *pubocervical ligaments*, and *uterosacral ligaments*. The principal support of the uterus is, however, the *pelvic floor* (pelvic diaphragm) which is composed of the two levator ani and the two coccygeus muscles. The muscles of the urogenital diaphragm and the perineal body provide further support for the uterus, hence damage to the perineal body during childbirth predisposes to uterine prolapse. Peritoneal folds, such as the broad ligaments, uterovesical and rectovaginal ligaments, do not contribute much to the support of the uterus.

### STRUCTURE AND FUNCTIONS

The uterine wall consists of three layers: *perimetrium*, *myometrium*, and *endometrium*. The perimetrium is the peritoneal covering of the uterus. It is firmly attached to the underlying myometrium everywhere except over the lower part of the anterior surface adjacent to the isthmus and on the posterior surface of the uterus in the region of the supravaginal cervix. Here it is separated from the muscular wall by loose areolar tissue and it can be easily stripped off from the uterus. This looseness of the peritoneum helps in adequate mobilization of the urinary bladder during operations. The muscular wall—or myometrium—of the uterus is composed of smooth muscle supported by connective tissue. The endometrium is the mucosal layer of the uterus. It is continuous with the lining of the uterine tubes superolaterally and with that of the vagina inferiorly. It consists of a single layer of columnar cells resting on a thick lamina propria made up of connective tissue called the endometrial stroma. Many tubular endometrial glands extend through the entire thickness of the endometrium and may occasionally penetrate the myometrium for a short distance. From puberty to menopause, the endometrium undergoes extensive changes during the menstrual cycle in response to ovarian hormones and is partly sloughed off each month during menstruation.

## APPLIED ANATOMY

The cervix and the body of uterus may be examined by bimanual palpation. With the bladder empty, the vaginal portion of the cervix is palpated with two digits of the right hand while the other hand is pressed inferiorly and posteriorly in the pubic region of the anterior abdominal wall. The size and position of the uterus can be determined in this way. In most women, the uterus is anteverted and anteflexed (Fig. 22.2). A retroverted, retroflexed uterus can be palpated through the posterior vaginal fornix.

The cervix normally has a firm consistency similar to the tip of the nose, but in the pregnant uterus it is soft and vascular. Similarly, there is softening of the isthmus of the uterus in pregnancy (Hegar's sign). A speculum examination allows the cervix to be visualized in order for microbiological and cytological samples to be taken and cervical procedures to be undertaken (Fig. 22.4).

The tone of the levator ani muscles is of great importance in supporting the uterus. Loss of tone may predispose to uterine prolapse.

## Uterine Tubes

### STRUCTURE

The two *uterine (fallopian) tubes* lie on either side of the uterus in the medial three-quarters of the upper free border of the broad ligament. This part of the broad ligament is called *mesosalpinx*. Each tube is 10–12 cm long and, for descriptive purposes, can be divided into four parts (Fig. 22.1b).

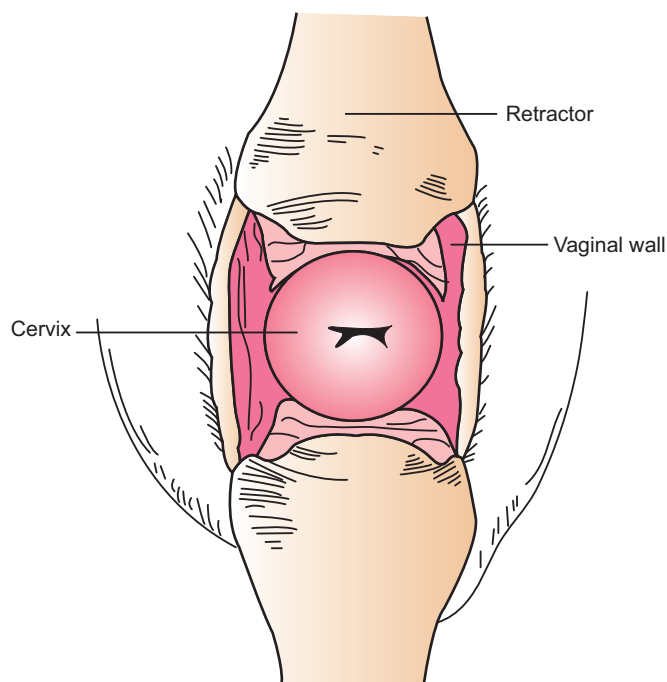


Fig. 22.4: View of the cervix during speculum examination.

- (i) **Infundibulum:** The lateral end of tube is 3 mm wide when relaxed and is funnel-shaped. Its opening or *ostium* is surrounded by finger like processes called the *fimbriae*.
- (ii) **Ampulla:** Extending for more than half the length of the tube, this thin-walled section of the uterine tube has a wider lumen and is the commonest site in which fertilization takes place.
- (iii) **Isthmus:** This is the medial third of the uterine tube. It is the narrowest part, 0.1–0.5 mm in diameter with the thickest muscular layer in its wall. The round ligament lies immediately anterior to this part of the tube and can be mistaken for it during laparoscopic sterilization.
- (iv) **Uterine (intramural) part:** This part of the tube pierces the myometrium and its narrow lumen, measuring only 1–2 mm in diameter, opens into the uterine cavity at the *uterine ostium*.

The uterine tube is composed of three layers—the *serosa*, the *muscular layer*, and the *mucosa*. The tubal mucosa is composed of secretory and ciliated columnar cells. It is invaginated to form folds called major plicae, with secondary and tertiary folds.

### BLOOD SUPPLY, LYMPHATIC DRAINAGE, AND INNERVATION

The arterial supply to the uterine tube is provided by tubal branches of the uterine and ovarian arteries. Venous drainage is provided by corresponding tubal branches which drain into the uterine and ovarian veins. Lymphatic vessels follow those of the uterine fundus and ovaries to ascend with the ovarian vein into the para-aortic lymph nodes. The nerve supply of the uterine tubes is derived from the ovarian and uterine plexuses. Afferent fibers from the tubes are contained in the T11, T12, and L1 nerve roots.

### FUNCTIONS

Once released from the ovary at ovulation, the oocyte is 'picked up' at the fimbriated, lateral end of the uterine tube. The action of the ciliated epithelium and contraction of the smooth muscle in its wall facilitate the movement of the oocyte toward the uterine cavity. Along the way, sperm, travelling along the conduit provided by the uterine tubes, may reach the oocyte. If fertilization takes place, the uterine tube additionally provides nourishment for the fertilized ovum and transports it to the cavity of the uterus.

### APPLIED ANATOMY

Sexually transmitted pathogenic bacteria may ascend through the uterus to enter the uterine tubes causing *salpingitis*. Because the female genital tract is in direct communication with the peritoneum, the infection may spread to cause a general *peritonitis*. Conversely, salpingitis may result from infection that spreads from the peritoneal cavity. Salpingitis may result in the formation of

adhesions which slow down the passage of the zygote and may result in a tubal ectopic pregnancy.

*Pyosalpinx* is the collection of pus in the uterine tube. *Hydrosalpinx*, a collection of fluid within the fallopian tube, is the result of occlusion of the tube by adhesions at both ends. It may be asymptomatic.

Tubal ectopic pregnancies are the commonest form of ectopic pregnancy. If not diagnosed early, they may result in tubal rupture and hemorrhage into the abdominopelvic cavity, which may constitute a threat to the mother's life.

Over 90% of female sterilization is done by ligation of the uterine tubes. Oocytes released from the ovary are prevented from coming into contact with sperm and die within the uterine tubes.

## Vagina

The vagina is a musculomembranous tube that extends upward and posteriorly from the vulva to the uterine cervix. It is 7–9 cm long and has anterior and posterior walls, which are normally in apposition except at its superior end where the anterior wall is pierced by the cervix, which in the majority of women, projects inferoposteriorly. The posterior wall is about 1 cm longer than the anterior wall. The upper half of the vagina lies above the pelvic floor and lower half lies within the perineum. The area of the vaginal lumen that surrounds the cervix is divided into four regions or fornices—anterior, posterior, right lateral, and left lateral.

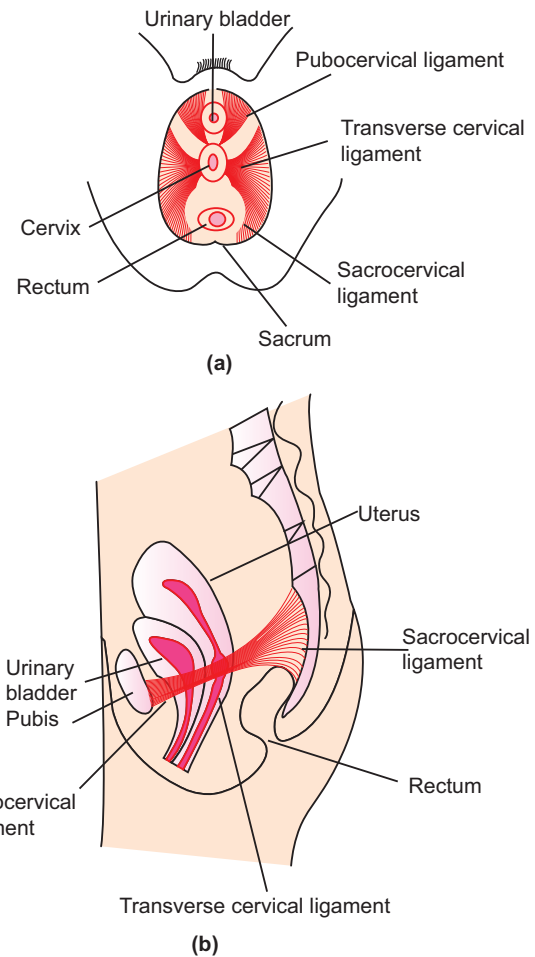
Anteriorly, the vagina is closely related to the bladder above and the urethra below. Posteriorly, its upper third is related to the pouch of Douglas and middle third, the ampulla of the rectum, and the lower third, the perineal body, which separates it from the anal canal. Lateral to the upper part of the vagina lie the ureters. The middle part of the vagina is related to laterally to the anterior fibers of the levator ani muscle as they run backward to reach the perineal body. Contraction of the fibers of levator ani muscle compresses the walls of the vagina together. The lower part of the vagina is related to the urogenital diaphragm and the bulb of the vestibule.

### SUPPORTS OF THE VAGINA

The principal supports of the upper part of the vagina are the transverse cervical, the pubocervical and uterosacral ligaments (Fig. 22.5). The lower part of the vagina is supported by the perineal body and the pubovaginal part of the levator ani muscle.

### BLOOD SUPPLY, LYMPHATIC DRAINAGE, AND INNERVATION

The *vaginal artery* is usually a branch of the uterine artery, although sometimes it arises from the internal iliac artery. The two vaginal arteries anastomose with each other and the cervical branch of the uterine artery. The vagina is additionally supplied by the internal pudendal artery and the vaginal branches of the



**Fig. 22.5:** Ligamentous supports of the uterus as seen from below (a) and laterally (b).

middle rectal artery. The vaginal veins form a plexus along the sides of the vagina and drain into the internal iliac veins. The lymphatic vessels from the upper third of the vagina drain into the external and internal iliac lymph nodes, the middle third to the internal iliac nodes, and those from the lower third to the superficial inguinal lymph nodes. The upper third of the vagina is supplied by autonomic nerves from the uterovaginal plexuses. The lower two-thirds have a somatic nerve supply from the pudendal nerve.

### STRUCTURE AND FUNCTIONS

The vaginal wall has three layers. The outermost is a thin layer of loose connective tissue with a rich plexus of blood vessels and occasional lymphoid follicles. Next, the muscular coat has outer longitudinal and inner circular layers of smooth muscle fibers. The mucous membrane is the innermost layer, consisting of stratified squamous, non-keratinized epithelium, it is devoid of glands. Due to the action of lactobacilli present in the vagina, vaginal transudates have an acidic pH of about 4.5 which protects the vagina from bacterial invasion. During infancy and after menopause, the vaginal acidity diminishes therefore bacterial



invasion may be more common. The epithelium gets keratinized when exposed to air, as occurs with significant degrees in uterine prolapse. The vagina not only is the female organ of copulation but also serves as the excretory duct for menstrual flow and forms part of the birth canal.

### APPLIED ANATOMY

During a *digital vaginal examination* (*per vaginal examination*), the uterine cervix is palpated superiorly, the ovaries and uterine tubes laterally, and the bladder, urethra, pubic symphysis anteriorly. The rectum may be palpated posteriorly (via the rectouterine pouch). The vagina may also be palpated by *digital rectal examination*. Here the index finger inserted into the anal canal facilitates the palpation (again via the rectouterine pouch) of the vagina and cervix and perineal body (Fig. 22.3).

A *cystocele* results from the bulging of the anterior vaginal wall due to slackening of support of the bladder. A *rectocele* results from the sagging of the ampulla of the rectum against the posterior vaginal wall.

Owing to the anatomical relationships of the vagina, any instrument directed posteriorly into the vagina may perforate the posterior wall and enter into the peritoneal cavity (via the rectouterine pouch). Peritonitis may subsequently ensue. Lacerations in the posterior fornix may also cause prolapse of the small intestine into the vagina.

*Uterine prolapse* is necessarily associated with some degree of sagging of the vaginal wall. A prolapsed uterus is graded based on level of descent: to the upper vagina (first degree), to the introitus (second degree), or external to the introitus (third degree or total, sometimes referred to as *procidencia*). Vaginal prolapse, the descent of the vagina, or vaginal cuff post hysterectomy, may be termed second or third degree.

### Female External Genitalia

The term *vulva* is the collective name for the female genitalia and includes the *mons pubis*, *labia majora*, and *minora*, *clitoris*, *vestibule*, the *greater vestibular glands*, the *orifice of vagina*, and *bulb of the vestibule* (Fig. 22.6).

The *mons pubis* is a rounded, hair-bearing elevation of skin, found anterior to the pubis. The pubic hair in the female has an abrupt horizontal superior margin, whereas in the male it extends upward to the umbilicus. The labia majora are prominent hair-bearing folds of skin extending posteriorly from the mons pubis to about 2.5 cm from the anus. Anteriorly they unite to form the *anterior labial commissure*. Posteriorly they are separated in the midline by the *posterior labial commissure*. Embryologically, the labia majora are homologous to the male scrotum.

The *labia minora* are two smaller, hairless folds of soft skin that lie between the labia majora. They consist of a core of spongy tissue with blood vessels and many sensory nerve endings. The labia minora enclose the vestibule and united posteriorly in the abrupt fold called the *fourchette*. Anteriorly they unite above the clitoris, forming an anterior prepuce or clitoral hood.

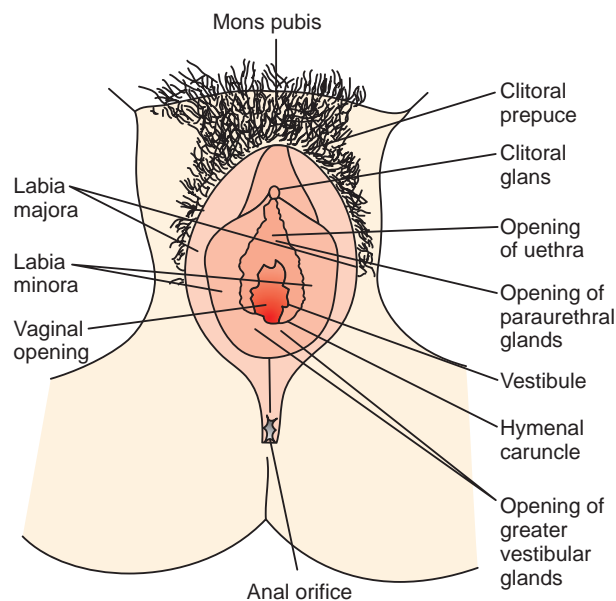


Fig. 22.6: Female external genitalia.

The *clitoris* is a small cylindrical erectile body rarely exceeding 2–3 cm in length. It is homologous to the male penis, but neither it is transversed by the urethra nor does it contain corpus spongiosum. The clitoris consists of a root and a body composed of two crura, two corpora cavernosa, and a glans (Fig. 22.7). The glans is less than 5 mm in diameter, is covered by squamous epithelium, and is partly hidden by the prepuce. It is richly supplied by nerves and is extremely sensitive.

The vestibule is the area bounded anteriorly by the clitoris, posteriorly by the fourchette, and on each side by the labia minora. It represents the urogenital sinus of embryo. It is perforated by openings of the urethra, vagina, ducts of the greater vestibular (Bartholin's) glands, and ducts of the paraurethral (Skene's) glands.

The vestibular bulbs lie beneath the mucus membrane of the vestibule on either side of the lower end of the vagina and the urethra (Fig. 22.7). Each is 3–4 cm long, 1–2 cm wide, and 0.5–1 cm thick. The vestibular bulbs consist of erectile tissue and are homologous to the bulb of the male penis. Unlike the penis,

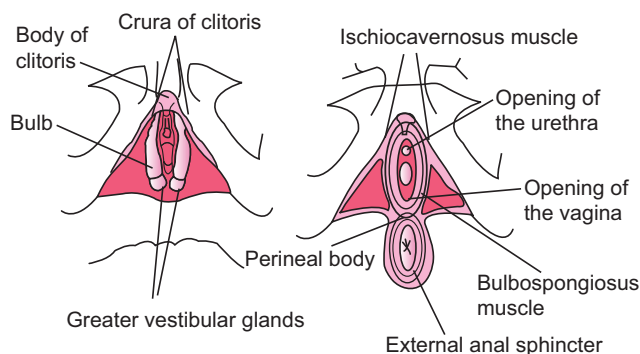


Fig. 22.7: Structures underlying the female urogenital triangle.



however, they are separate from the clitoris and separated from one another by the vestibule. Their posterior ends are expanded and are in contact with the greater vestibular glands. They may be injured during childbirth or episiotomy, and may give rise to hematoma of the vulva or cause profuse hemorrhage.

The female urethra is 3–4 cm long. It extends from the neck of the bladder to the external urethral meatus, where it opens into the vestibule about 2.5 cm below the clitoris. The orifice is usually puckered and appears as a vertical slit with slightly raised margins. At the sides of the urethral opening are the small openings of the ducts of the paraurethral (Skene's) glands. These are a pair of small mucous glands lying on each side of the lower end of the urethra. They are homologous to the prostate in men. The ducts of these glands open usually in the vestibule on either side of the urethra but may open inside the posterior urethral wall just inside the urethral opening. The opening of each duct is only 0.5 mm in diameter.

The greater vestibular glands or Bartholin's glands are a pair of round or oval bodies, measuring about 0.5–1 cm in diameter. They lie partially overlapped by the vestibular bulb posterolateral to the vaginal orifice (Fig. 22.4). These glands are homologous to the male bulbourethral (Cowper's) glands. Slender ducts, about 2 cm in length, open from either gland into the vestibule in the groove between the hymen and the posterior part of the labium minus. Clear or whitish mucus is secreted by these tubuloalveolar glands in response to sexual stimulation. These glands have been demonstrated to have cells with endocrine function, which secrete serotonin, calcitonin, bombesin, ketacalcin, and human chorionic gonadotrophin. The glands are frequent sites of an abscess or cyst formation (Fig. 22.8).

The vaginal orifice is located in the posteroinferior part of the vestibule and varies considerably in shape and size. The hymenal remnant is a thin fold of mucous membrane surrounding the vaginal orifice.

### BLOOD SUPPLY, LYMPHATIC DRAINAGE, AND INNERVATION

The vulva has a rich arterial blood supply arising from the branches of the external pudendal artery, a branch of the femoral artery, and branches of the internal pudendal artery.



Fig. 22.8: Bartholin's cyst.

Corresponding veins drain into the external and internal pudendal veins. The anterior parts of the vulva including the mons pubis are innervated by the ilioinguinal and genitofemoral nerves. The posterior parts of the labia and the perineal region are supplied by the labial branches of the perineal nerve, a branch from the pudendal nerve, and perineal branches of the femoral (posterior) cutaneous nerve of the thigh. The vulva has rich lymphatic network. Lymphatics from the vulva, perineal skin, and the lower part of vagina drain into the medial group of superficial inguinal lymph nodes, while lymphatics from the clitoris and deep structures drain into the deep group of inguinal and internal iliac lymph nodes.

### APPLIED ANATOMY

The presence of numerous glands and ducts opening onto the surface of the vulva renders this area prone to infection. The sebaceous glands of the labia majora, the greater vestibular glands, the urethra, and the paraurethral glands can all become infected.

In pregnancy, the vulval appearance may change to reveal a bluish discoloration as a result of venous congestion. This appears between the 8th and 12th weeks of gestation and increases as the pregnancy progresses.

Cystitis is much more common in females than in males owing to the short length of the female urethra which predisposes to ascending infection. Catheterization is also easier in females than in males because the female urethra is shorter, wider, and more dilatable. Moreover, the urethra is straight and only minor resistance is felt as the catheter passes through the urethral sphincter.

Due to the rich arterial supply to the vulva, hemorrhage from vulval injuries may be severe. During parturition, the most pain is usually felt when the fetal head passes through the vulva due to stretching of its parts. A pudendal nerve block can be used for anesthesia during child birth, where local anesthetic is injected around the pudendal nerve supplying this area.

An episiotomy is an incision made in the perineum to permit delivery of the fetus without perineal laceration.

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# Normal Genital Flora

Frances E. Keane

## Introduction

Although the intrauterine environment is completely sterile, from the time of delivery the neonate is exposed to a multitude of organisms from sources such as the birth canal and the hands of carers. Thus, gradually the skin, oropharynx, gastrointestinal tract, and other mucosal surfaces become colonized by microbes. The vagina and cervix, as well as the urethra in both sexes, have an established microflora. Although this chapter will refer to the other sites, its focus will be the endogenous vaginal flora as evidence accumulates for its protective role against the development of bacterial vaginosis (BV), the main cause of abnormal discharge in women of childbearing age, and the acquisition of sexually transmitted infections, including HIV.<sup>1</sup>

## Female Genital Flora

### VAGINAL FLORA

There have been many studies of the endogenous flora of “normal women” however, these should be interpreted with some caution as the definition of “normal” varies between studies as do the methods employed to identify and quantify bacteria. Collectively, the available studies provide a useful overview regarding trends of species colonization; however, it is widely acknowledged that the full spectrum of organisms comprising the healthy vaginal flora has yet to be described.<sup>2</sup>

In healthy women of child-bearing age the vagina is an acid environment, although transient elevations in pH are created during events such as coitus, by the introduction of sperm, and menstruation. In 1894, Doderlein published his definitive study describing Gram-positive bacilli (rods), subsequently named *Lactobacillus* spp., as the dominant constituents of the vaginal flora of healthy women.<sup>3</sup> However, it was later realized that although lactobacilli dominate, the normal vagina contains a mixed flora including other facultative (replicating in the presence or absence of oxygen) and strictly anaerobic organisms. Quantitative studies have reported isolation of facultative lactobacilli in up to 96% of healthy volunteers.<sup>4,5</sup> Over time, opinion has varied

as to which species of lactobacilli predominate; early studies reported *L. acidophilus* and *L. fermentum* to be most commonly isolated.<sup>6,7</sup> However, subsequent use of DNA homology and other nucleic acid technologies have confirmed *L. crispatus* and *L. jensenii* to be the predominant species in the healthy vagina.<sup>8,9</sup> Other less commonly isolated Gram-positive bacilli include *Eubacterium* spp., *Bifidobacterium* spp., *Propionibacterium* spp., and *Clostridium* spp.<sup>10</sup>

The second commonest isolates from the normal vagina are Gram-positive cocci. These include facultative anaerobic organisms such as coagulase-negative staphylococci and streptococci, including group B beta-hemolytic streptococci and *Enterococcus* spp.<sup>11</sup> Anaerobic Gram-positive cocci have also been isolated in up to 80% of pre-menopausal women, the most common being *Peptostreptococcus asaccharolyticus* and *P. prevotti*.<sup>12</sup>

Gram-negative rods are also isolated from the healthy vagina in up to 40% of women; these include *Gardnerella vaginalis* and *Bacteroides* spp. *Fusobacterium* spp. and *Mobiluncus* spp. are much less frequently isolated from healthy women.<sup>12–15</sup> Interestingly, *G. vaginalis* was first described by Gardner and Dukes in 1955, as the sole and unique causative organism of “non-specific vaginitis,” subsequently renamed BV. However, BV is now recognized as a condition of mixed flora in which the organisms mentioned above are found in greater numbers than in women with healthy vaginal flora.<sup>15</sup> Other Gram-negative rods isolated infrequently from the healthy vagina include *Enterobacteriaceae* spp., *Escherichia coli*, and *Klebsiella* spp.<sup>4</sup>

Gram negative cocci, such as *Veillonella* species, are infrequently isolated from the healthy vagina.<sup>15</sup> Other organisms, such as *Mycoplasma hominis* and *Ureaplasma urealyticum*, both of which lack cell walls, are common constituents of the vaginal flora, yet both are isolated in smaller numbers from healthy women compared to those with BV.<sup>15,16</sup> *Candida albicans* is the most common yeast isolated from the healthy vagina.

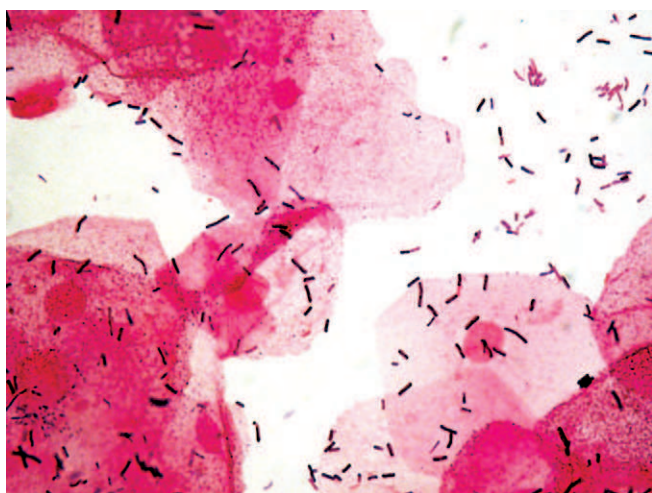
In the clinical setting, microscopy of Gram-stained vaginal samples provides a cost-effective and relatively straightforward method of obtaining a “snapshot” of the vaginal flora. This provides an extremely useful near-patient diagnostic test to assist in the



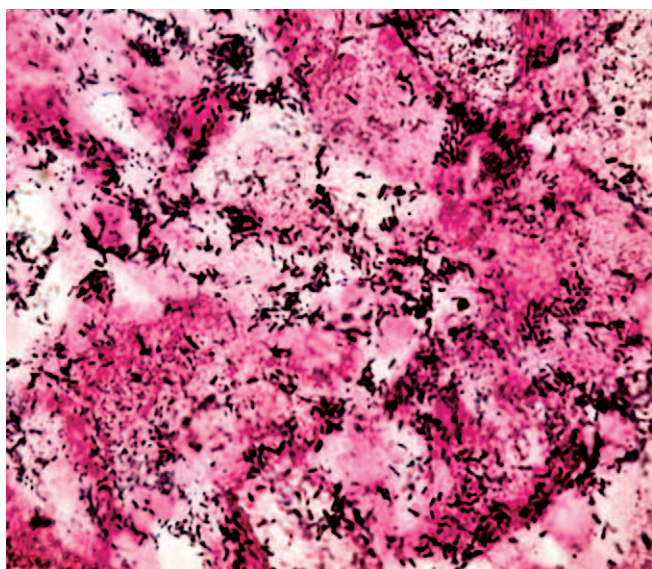
diagnosis of women presenting with vaginal discharge, particularly those with BV. The Ison–Hay classification method<sup>17</sup> describes five different categories of vaginal flora and has compared well against more complicated scoring systems. The five categories are: grade 0, epithelial cells only with no bacteria present; grade 1, normal, *Lactobacillus* spp.-dominated flora; grade 2, intermediate flora with reduced numbers of lactobacilli and mixed flora; grade 3 (BV), mixed bacterial flora only; and grade 4, Gram-positive cocci alone. Illustrations of normal vaginal flora can be seen in Figures 23.1 to 23.3.

## Factors Influencing the Vaginal Flora

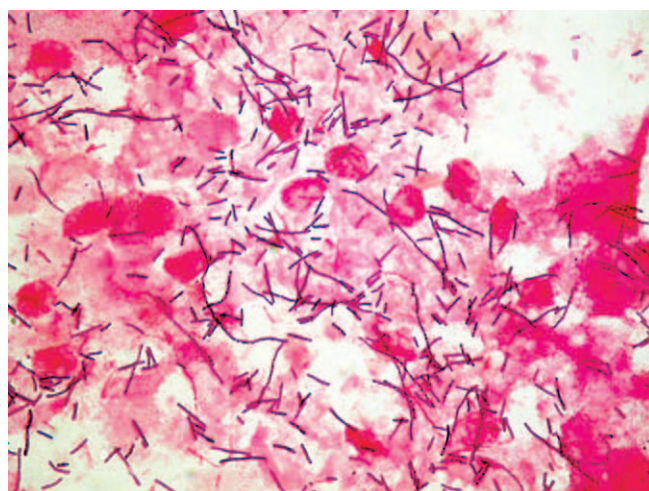
The vaginal flora is subject to many influences, including hormonal status, menses, contraceptive practices, and sexual activity.



**Fig. 23.1:** *Lactobacillus* morphotypes (Gram-positive [purple] rods) on a background of epithelial cells. Courtesy: Dr. Richard Bendall.



**Fig. 23.2:** Short *Lactobacillus* morphotypes. Courtesy: Dr. Richard Bendall.



**Fig. 23.3:** Mixed *Lactobacillus* morphotypes, including some long forms. Courtesy: Dr. Richard Bendall.

## Hormonal Status

The hormonal status of women varies under the influence of age, the transient shifts of the menstrual cycle, and the use of exogenous hormones in both contraceptives and hormone-replacement therapy.

## Age-Related Effects

For the first 3 or 4 weeks following delivery, the neonatal vagina is under the influence of maternal estrogen; the vaginal epithelium is anatomically and physiologically similar to that of the mother and facultative lactobacilli predominate.<sup>18</sup> Thereafter, maternal estrogen is gradually metabolized, the vaginal epithelium exfoliates, acid production is lost and the vaginal pH rises. Facultative lactobacilli are lost and are replaced by skin commensals such as coagulase-negative staphylococci and fecal organisms such as *E. coli*. With the onset of puberty, the vagina is subject to the influence of estrogen once more, the glycogen content is re-established, lactic acid is produced by glycogen metabolism and the healthy vagina is colonized by a *Lactobacillus*-dominated flora. At menopause, the vaginal appearance gradually reverts to that of pre-menarche in women not on estrogen replacement therapy. Facultative lactobacilli are isolated in less than 50% and *G. vaginalis* and genital mycoplasmas are also less frequently isolated.<sup>19</sup>

## Menstrual Cycle

An early quantitative, sequential study of vaginal flora over the menstrual cycle reported a sharp pre-menstrual decrease in concentrations of facultative microbes and a constant concentration of anaerobes throughout the cycle.<sup>12</sup> Other workers reported no overall decrease in the concentration of bacteria although anaerobic lactobacilli predominated during menses and facultative lactobacilli in the remaining three weeks.<sup>20</sup> The greatest species diversity occurred during menses. A subsequent,

larger study reported a slight decrease in the rate of recovery of *Lactobacillus* species during menses and a decrease in the prevalence of other species outside that time.<sup>21</sup>

Studies of sequential, Gram-stained, vaginal samples over the menstrual cycle reveal a variety of patterns of vaginal flora, that is, normal flora throughout, abnormal flora throughout, and either predominantly normal or abnormal flora that undergoes a transient shift.<sup>22–24</sup> In all studies, transient shifts toward an abnormal flora occurred around the time of menses. During menses the vaginal pH undergoes a temporary elevation but the true reasons for the shifting patterns of vaginal flora are poorly understood. The published data on the use of catamenial products suggest that there is no sustained difference in vaginal populations of facultative and anaerobic organisms between users of tampons and sanitary towels.<sup>25</sup>

### Pregnancy

There are conflicting data regarding the effect of pregnancy on the composition of vaginal flora. Some workers report that women with abnormal flora in early pregnancy have a tendency to revert to normal as pregnancy progresses,<sup>26</sup> but other studies, albeit of shorter duration, have produced conflicting results.<sup>27</sup> However, it remains undisputed that abnormal vaginal flora, particularly BV, is associated with an increased risk of pre-term labor and other adverse pregnancy outcomes.

### Hormonal and Other Types of Contraception

The combined oral contraceptive pill and consistent condom use appears to promote maintenance of the normal vaginal flora.<sup>28,29</sup> While some workers<sup>28</sup> have reported progesterone-only methods to be protective of the normal flora, others<sup>30</sup> suggest progesterone-only contraception produces a hypo-estrogenic state and a reduction in hydrogen peroxide ( $H_2O_2$ )-producing *Lactobacillus* spp., whose protective effects are described below. The use of the copper intrauterine contraceptive (IUCD) device is strongly associated with a change in the vaginal ecosystem to the detriment of facultative lactobacilli<sup>29</sup>; however, there is no available information on the effect of the progesterone-incorporated intrauterine system. The effects of the spermicide nonoxynol-9 are incompletely understood, although there is evidence to suggest that it may adversely affect the lactobacillus population.<sup>31,32</sup>

### Sexual Activity

The introduction of sperm causes a rise in vaginal pH, which can take up to 8 hours to return to normal.<sup>33</sup> A recent meta-analysis<sup>34</sup> reported an association between the loss of a *Lactobacillus*-dominated flora and sexual contact with new and multiple male partners. A similar association is found with exposure to female sexual partners.

Smoking<sup>35</sup> and genital hygiene practices, such as douching,<sup>36</sup> have also been associated with disruption of the normal vaginal flora.

## Protection Against Infection

Microbes can migrate to sterile areas, such as the uterus, ureters, and kidneys, causing disease; however, they face many challenges in order to do so. These include crossing either external keratinized epithelium or internal mucosal epithelial layers, the latter being covered by a thick mucus layer that is colonized by commensal microbes. Further obstacles include the innate immune system at epithelial surfaces, comprising cells with the capacity to express antimicrobial agents or mount a rapid antimicrobial response utilizing, for example, macrophages and natural killer cells. Additional defense mechanisms include antibody production and T cell activation at mucosal surfaces.<sup>37</sup>

As the dominant vaginal commensals, lactobacilli have a key protective role against colonization by both endogenous and exogenous pathogens, particularly with respect to the development of BV. *In vitro* studies have demonstrated the ability of lactobacilli to inhibit the growth of many species such as *G. vaginalis*, *Mobiluncus* spp., and *Bacteroides* spp.<sup>38</sup> Various methods of protection by endogenous lactobacilli have been proposed, among them the production of lactic acid as a by-product of *Lactobacillus* metabolism, thus contributing to the maintenance of a low vaginal pH. Furthermore, some *Lactobacillus* spp. produce  $H_2O_2$  which has demonstrated toxicity to *G. vaginalis* and *Prevotella bivia*, an effect enhanced by the addition of peroxidase and halide, both of which occur naturally in human secretions.<sup>39</sup>  $H_2O_2$ -producing *Lactobacillus* spp. are more prevalent in women of childbearing age than in pre-menarchal or post-menopausal women.<sup>40</sup> They have also demonstrated the ability to kill HIV *in vitro*.<sup>41</sup> The exact function of bacteriocins, also produced by  $H_2O_2$  lactobacilli, is unknown.

### CERVICAL FLORA

The cervix sits within the vagina and thus might be assumed to host identical resident microflora, but it does provide a different micro-environment to its vaginal counterpart. For example, while the vagina is of acid pH, that of the cervix is more neutral. In addition, while the surface of the vagina is covered purely by stratified squamous, nonkeratinizing, epithelium, as is the ectocervix, the endocervical canal is covered by columnar epithelium. The position of the squamo-columnar junction is under hormonal influence and may therefore be hidden inside the endocervical canal, or extend out over the ectocervix, typically in women who are pregnant or using the combined oral contraceptive pill. Comparison of the cervical and vaginal microflora suggests that although the patterns of aerobic and anaerobic bacteria isolated from both sites are similar, considerable differences are observed between paired samples from the same woman.<sup>42</sup>

### URETHRAL FLORA

Studies of healthy women have confirmed that the urethra, like the vagina, is colonized predominantly by *Lactobacillus* spp. and staphylococci.<sup>43</sup> However, in women prone to recurrent urinary



tract infections, Gram-negative enteric bacteria, mainly *E. coli* have been found to dominate the urethral flora.<sup>44</sup>

## Male Genital Flora

There have been fewer studies of the normal male genital flora. Bowie et al.<sup>45</sup> compared men with and without urethritis and reported that aerobic lactobacilli, *G. vaginalis*, alpha-hemolytic streptococci, and anaerobes, predominantly *Bacteroides* spp., were more likely to be isolated from men without, than from those with, urethritis. In a more recent, semi-quantitative study<sup>46</sup> of 30 uncircumcised men, samples obtained from the external urethral orifice, navicular fossa, and penile urethra revealed the flora to be dominated by Gram-positive aerobic bacteria, with the most common species identified being staphylococcus coagulase-negative spp., group viridans alpha-hemolytic streptococci, *Corynebacterium* spp., and *Enterococcus* spp. A variety of *Malassezia* and, to a lesser extent, *Candida* yeasts are also isolated as part of the resident male genital micro flora in both circumcised and uncircumcised men although colonization patterns may vary according to circumcision status.<sup>47,48</sup> In another study from the urethra of 50 sexually inexperienced adolescents: aerobes (66%), *Staph. epidermidis* (28%) and diphtheroids (20%) etc. were the predominant isolates with hardly any potential pathogens: ureaplasma in 4% and Gardnerella in 2% only.<sup>49</sup> Male circumcision has been shown to reduce carriage of uropathogenic organisms by young boys.<sup>50</sup>

## Conclusion

The genital ecosystem is an intricate and dynamic environment, subject to many potential influences. Although a plethora of studies have already been undertaken, the composition of genital flora has not yet been completely elucidated. This is an area of understanding that should improve over the coming years with the advent of new technologies for the detection of organisms. In addition however, we need to gain a greater understanding of how endogenous flora operate within the complex host immune system and other organisms achieve pathogenic status before we can best appreciate how to prevent genital infection.

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# 24

## History and Physical Examination

Keith Radcliffe

### Introduction

As in all medical consultations, the combination of taking history from the patient and performing physical examination forms the cornerstone of the management of a person presenting because of concerns relating to sexually transmitted infections (STIs). In addition, the obtaining of appropriate samples for specialized microbiological investigations will often be done in the course of the physical examination. Even where a diagnosis of STI is unlikely, and no abnormalities are found on examination, the mere fact of having been carefully examined by a trained practitioner will often be very reassuring to an anxious patient.

Each consultation represents a unique event, and the manner in which it is conducted will be influenced by a variety of factors, including the cultural and religious background of the patient, and the prevailing legal, professional, ethical, and regulatory frameworks in operation. However, certain universal principles will always apply, very importantly those relating to privacy and confidentiality, and the right to have their dignity respected. The right to privacy is enshrined in Article 12 of the Universal Declaration of Human Rights: "No one shall be subjected to arbitrary interference with his privacy ..." <sup>1</sup> In all cultures sexual relations are held to be a private matter, and confidentiality in this field is therefore always of utmost importance. This has been recognized by the World Medical Association, which has stated that: "The physician shall respect a patient's right to confidentiality," and that a breach of confidentiality can only be justified when "... there is a real and imminent threat of harm to the patient or to others and this threat can be only removed by a breach of confidentiality." <sup>2</sup> Practical implications of this are that whenever possible, only the practitioner and the patient should be present during the consultation, and that steps be taken to prevent the consultation being overheard. Ideally it should be conducted in a private room which is adequately soundproofed, and the doors should be kept closed. All efforts should also be made to minimize interruptions. Sometimes another person may be present, for example, a trainee healthcare worker, an interpreter, or a family member. With regards to the presence of trainees, it

should be noted that the World Medical Association has stated that: "The patient has the right to refuse to participate in ... the teaching of medicine." <sup>3</sup> Therefore, the patient's permission for a trainee to be present during the interview should be obtained in advance without duress. The presence of family members, partners, or spouses during the consultation can also be problematic. The patient should be asked if they wish this person to be present, as their being there may be a barrier to obtaining a full and frank history, particularly in relation to sexual activity. If asked in the presence of the family member or partner, the patient may feel too embarrassed to refuse, so whenever possible they should be asked about their wishes with regard to this in private. Another complication that may arise is that a family member or partner may ask to act as interpreter. Again this may be a barrier to obtaining an accurate history, and every effort should be made to utilize an interpreter who is unknown to the patient.

It is important to realize that there is no single best way to conduct the history and examination. Each individual practitioner will inevitably develop their own habitual style over time. It is worth paying some attention to this, as developing a logical routine will improve the efficiency of the process, and lessen the possibility of omissions. This may be aided by the design and use of stylized pro formas for recording the essential elements of the history and examination, and this can be extended to include a note of the routine laboratory investigations requested, and the results of these when they are received. It is also important not to become a slave to routine. Although many consultations may follow a rigid pattern, the questions asked and the elements of the examination need to be tailored to the clinical situation, with particular regard to the presenting complaint, knowledge about exposure to sexual partners with specific conditions, and the local epidemiology of various infections. For example, a particular examination will naturally and quite rightly often be focused on the patient's anogenital area, but this may need to be extended, for example, to examination of mucocutaneous surfaces and palpation for lymphadenopathy in a person exposed to a contact with syphilis. The practitioner must also be flexible and be prepared to break off from his normal routine, in particular

when unusual responses are given to his questions. Finally, this chapter must be read in conjunction with other chapters in this book which address individual conditions in detail.

## Taking History

The questions should be asked in a systematic way, leaving the most sensitive ones (those relating to sexual activity) until later on. Traditionally the questions are asked in a face-to-face interview with a healthcare professional but in recent years innovative ways of obtaining the information have been developed. Asking the patient to complete a questionnaire prior to seeing the clinician would appear to be as good at eliciting the necessary information as the traditional interview.<sup>4</sup> Similarly, computer-assisted structured interviews, where patients enter the information directly into a computer in response to questions asked on screen or on audio, also appear to work well.<sup>5-7</sup> These approaches must be adapted to the local situation and may work better in some cultural contexts but less well in others. Issues of literacy and language skills are obviously important and systems must be in place to identify and assist those with problems in these areas.

If the history is obtained by questionnaire or computer then this is as a prelude to being seen by the clinician, and not a replacement for the consultation. The clinician will often need to expand upon the information obtained as required and might need to check and correct some of it.

The questions that need to be asked are for several distinct purposes:

- To establish the reason for the visit, in particular whether the patient has symptoms and if so what these are,
- To obtain details of recent sexual activity in order to decide what samples are required for microbiological (and possibly other) tests,
- To obtain information about risk behaviors for blood-borne viruses (HIV, hepatitis B and C) to inform choice of investigations, and to provide a basis for advice on reducing risk in the future, and
- To obtain general medical, gynecological, obstetric, menstrual, and contraceptive histories to inform decisions about investigation and management.

The following areas need to be addressed:

**Presenting complaint(s):** The reasons for the patient seeking a consultation about STI is best begun with a general, open question along the lines of: "What is the problem?" or "What can I do for you?" The practitioner should interject with additional questions to clarify statements made by the patient, and to seek further information as necessary. A degree of direct questioning will usually be necessary to inquire about symptoms suggestive of STI. This will require questions about specific symptoms localized to the genital tract, and also possibly related to systemic presentations of STIs, for example, weight loss, fever, skin rash, red eyes, night sweats, etc.

**Past medical history:** Firstly, relating to previous episodes of STI (obtain details about definite diagnoses, including when, where,

and how treated). Remember to enquire specifically about history of jaundice and vaccination against hepatitis B virus infection. Secondly, about significant past general medical problems, in particular, illnesses requiring hospitalization, surgery, or long-term treatment by a physician. Establish whether the patient is on any regular medications (and if so obtain details), whether they have received recent treatment with antimicrobials (say within the last month), and whether they have experienced allergic reactions to any prescribed medications.

**Family history:** Ascertain the patient's place of birth and upbringing. This is relevant in cases of suspected congenital syphilis, as this is more likely if the mother did not receive adequate antenatal care. It also has a bearing on the possibility of non-venereal treponematoses, hepatitis, and HIV infection, as these conditions are more likely if the person grew up or became sexually active in an area of high endemicity for these conditions.

**Gynecological history:** Menstrual history is important as this will have a bearing on possible pregnancy in women who have had unprotected sexual intercourse since their last menses. Also, symptoms related to the upper female genital tract, such as deep dyspareunia, intermenstrual bleeding, menorrhagia, and dysmenorrhoea, may suggest pelvic infection. The obstetric history is also important, both because a history of miscarriages may suggest prior infections (e.g., syphilis), and female patients may have been screened for various blood-borne sexually transmitted agents as part of past routine antenatal care, for example, hepatitis B and C virus infections, HIV, and syphilis. The woman's contraceptive history is important in excluding pregnancy, and she should also be asked about cervical cytology, especially where this is recommended as part of a national or local screening program

**Sexual history:** Always be aware of the need to establish the patient's sexual orientation beyond any possibility of confusion. It is always too easy to assume that the person is exclusively heterosexual. Enquire about recent sexual partners, extending back at least three months and possibly one year, as is deemed appropriate in the individual case. Obtain details concerning the date of the last coitus, the length of the sexual relationship, the type of sexual activity (particularly the type of penetrative intercourse that took place, specifically oral, anal, and vaginal penetration). Establish whether condoms have been used infallibly with each sexual partner. This requires that condoms should have been used for every act of penetrative intercourse, and for them to have been used properly, that is, for no penetration whatsoever to have occurred without a condom in place, and that the condom did not break or slip off during intercourse. Ask whether each partner is known to have complained of any symptoms that might suggest a diagnosis of a STI. Also enquire as to the country and region of upbringing of the partner, as this may influence the likely risk of individual STI, according to knowledge of their epidemiology in those areas. When obtaining a detailed sexual history for recent partners in this way, it is also worthwhile enquiring about the total number of sexual partners in the medium term, say in the last 12 months, as this helps to gauge the person's risk of having contracted an STI.



**HIV risk assessment:** Activities known to be associated with an increased risk of acquisition of HIV should be specifically enquired about. These include involvement in prostitution, male homosexuality or bisexuality, having injected drugs, sexual partners from areas of high endemicity, history of transfusion with blood or blood products, and sexual contact with intravenous drug users or (in the case of females) hemophiliac or bisexual male partners. Note that these factors will often indicate an increased risk of having been exposed to STIs other than HIV as well. It is important to remember that negative responses to these questions will not eliminate the need to consider testing for HIV infection, and this will be particularly true in areas where HIV transmission among the general heterosexual population is known to be frequent. Ask whether the patient has previously been tested for HIV, and if so, when and where this was carried out.

**Social history:** Ask about home and family circumstances, including nature of employment if any.

## Performing Physical Examination

It is not necessary to carry out a physical examination in all cases where a consultation is sought because of concerns about STI. As a general rule, the examination may safely be omitted in patients who report no symptoms. This is not only because examination of asymptomatic individuals is unlikely to be productive<sup>8–10</sup> but also advances in diagnostics mean that samples can be obtained non-invasively, obviating the need for a physical examination. Testing for chlamydia and gonorrhea can be done by using: urine samples for men<sup>11</sup> and women,<sup>12</sup> self-taken vaginal swabs for women,<sup>13,14</sup> and self-taken pharyngeal and rectal swabs for men who have sex with other men.<sup>15</sup>

In some cases it might be indicated to carry out a physical examination even in the absence of symptoms if the clinician believes that the patient is at high risk of STI. This likely to be because they are in a high-risk group, such as men who have sex with men or commercial sex workers, or because they give a history of sexual contact with an infected partner. It is not possible to be dogmatic on this point, since the clinician must exercise a judgment based upon their knowledge of the probability of disease in their own individual practice.

Consideration should always be given to having another member of staff present as a chaperone when carrying out an intimate physical examination on the patient. This applies whatever the genders of the practitioner and the patient. This meets several different needs: it reassures the patient, the chaperone is usually a nurse or other healthcare worker who is able to assist the practitioner in carrying out the examination, it provides a witness as protection against allegations of indecency or impropriety. The desirability of always having a chaperone present may have to be balanced against the resource implications, in that a member of staff may not always be available to act in this role.

The physical examination of both male and female patients is best carried out with the patient in the supine position. Attention should be paid to the position of both the patient and practitioner,

for example, in ensuring that the couch the patient lies on is at the optimal height for the procedure to be carried out. Bright lighting is required, and one source of this should be sufficiently flexible to allow illumination to be directed at the area under examination. It should go without saying that the examination room should be private and adequately sound-proofed; cubicles partitioned off by curtains are unsuitable, as any necessary conversation conducted during the examination can easily be overheard by third parties. Ensure that all necessary equipment and materials are to hand and laid out in a systematic way such that the examination can proceed with smooth efficiency from start to finish. It is desirable that the practitioner wear surgical gloves when carrying out the examination of the anogenital area. Such attention to hygiene is reassuring to the patient, and, also has the benefit of protecting the practitioner from possible infection, for example, from the infectious lesions of early syphilis. It is also important to ensure adequate exposure when examining the patient's anogenital area. If male patients do not remove all clothing from the lower half of the body, then trousers and underwear should be lowered to the knees or below. Women will need to be exposed from the waist down, as will men if proctoscopy is to be performed. As the examination proceeds talk to the patient, in straightforward language that they can understand, about what you are going to do. When appearances and findings are normal, provide continuous verbal reassurance to the patient that this is the case.

## GENERAL EXAMINATION

The need to extend the physical examination beyond the anogenital area should be guided by: symptoms complained of by the patient in the history, knowledge of the diagnosis in the patient's sexual partners, the patient's sexual history, and local epidemiology of specific conditions. Examples of STI which may have systemic presentations distant to the anogenital area are: HIV infection, secondary or tertiary syphilis, disseminated gonococcal infection, acute hepatitis B virus infection, and secondary lymphogranuloma venereum. Always remember that measuring the patient's vital signs, especially pulse rate and temperature, may also be very useful in such situations. At the end of the physical examination, consideration should be given to performing urinalysis for glycosuria. This is not indicated in asymptomatic patients but should be performed in cases of vulvitis or balanitis, as genital infection with candidiasis is a not infrequent mode of presentation of diabetes mellitus.

## Examination of Male Patient

### GENITAL EXAMINATION

Careful inspection of the genital and perigenital areas should be carried out and any cutaneous lesions noted carefully. Both inguinal areas should be palpated for lymphadenopathy. If enlarged lymph nodes are palpated, then attention should be paid to their number, size, and tenderness. Remember that not all swellings in the groin will be infective in origin (e.g., inguinal hernia, lymphatic

spread from carcinoma, and lymphoma) and that not all infective causes of inguinal lymphadenopathy will be due to STIs (e.g., plague, tularemia, and tuberculosis). Next, all surfaces of the penis should be carefully inspected. In an uncircumcised male the prepuce should be fully retracted to allow the subpreputial area, the coronal sulcus, and the glans penis to be visualized. Pay careful attention to the external urinary meatus for genital abnormalities, such as hypospadias, epispadias, and urethral duplication. Note the presence of any urethral discharge and if present, its volume and character (mucoid, mucopurulent, or frankly purulent). If no discharge is seen then “milk” the urethra by moving the fingers of one hand along the length of the underside of the penis while steadying the shaft of the penis in the other hand. This will express any secretions present in the urethra and render them visible at the meatus. If urethral samples are to be sent for microbiological investigations, then these should be obtained at this stage. Palpate the penis for indurations due to fibrous plaques of Peyronie disease or the presence of foreign bodies, strictures, periurethral abscesses, or urethral tumors. Next, examine the scrotum. Firstly, inspect the skin of the scrotum, noting, for example, prominent sebaceous glands which are often a source of anxiety to patients which can be addressed through strong reassurance. There may also be lymphedema, for instance in late lymphogranuloma venereum. Next, palpate the contents of the scrotum, paying particular attention to both testes and epididymis (which are located posterior to the testes). Bimanually examine both of these structures on each side. Note the presence of any mass. There are various causes for such a finding including, malignancy (the mass tends to be smooth or nodular, and painless), a gumma of the testis in tertiary syphilis, tuberculous involvement of the epididymis or testis<sup>16</sup> (hard and non-tender). Use a small torch to determine whether any mass present transilluminates. If it does then this suggests a benign cystic structure, such as a hydrocele or spermatocele. The absence of a testis suggests cryptorchidism or an abnormally retractile testis in an adult. Sometimes a testis is unusually small; if it is soft in appearance then this may indicate atrophy which could be congenital or the result of previous infection (especially mumps) or surgery (e.g., for herniorrhaphy, undescended testis, or torsion of the testis). Bilateral atrophic testes may indicate Klinefelter syndrome, which affects 0.2% of men leading to infertility and is a result of the presence of abnormal sex chromosomes (XXY). A unilateral painful swelling may be due to torsion of the testis and this must always be considered in the young adult as it represents a surgical emergency in which unnecessary delay may lead to serious adverse consequences. Or it may be a result of epididymo-orchitis, in which case there may also be an accompanying hydrocele. Epididymo-orchitis may be due to: an STI (especially chlamydia infection or gonorrhea), as a complication of a urinary tract infection, due to a viral infection (especially mumps),<sup>17</sup> or as a side-effect of medication (e.g., amiodarone). Rarely, a unilateral painful swelling results from a twisted appendix testis. Palpate the neck of the scrotum on each side between the finger and thumb; it should be possible to palpate the spermatic cord. Swellings in this area are usually due to hernias, hydroceles, or varicoceles. Varicoceles are due to enlarged

veins giving a “bag of worms” sensation on palpation, and usually disappear when the patient is recumbent.

## EXAMINATION OF ANORECTUM

Inspection of the perianal area should be carried out in male patients if they have symptoms. Perianal warts may be present in men<sup>18</sup> (and women) who are exclusively heterosexual. The examination is best done after examination of the genital area has been concluded. Ask the patient to roll into the left lateral position and to draw both knees up towards their body, but keeping their legs together and in contact with the couch. Separate the buttocks using both hands to allow inspection of the perineum and perianal areas. Make careful note of any lesion seen. These may indicate the presence of STI (e.g., condylomata acuminata due to infection with human papillomavirus, condylomata lata in secondary syphilis, or ulceration due to herpes simplex virus infection), or due to other pathologies (e.g., hemorrhoids, anal fissure, or fistula). Digital rectal examination should now be performed if indicated by symptoms suggestive of prostatic disease, that is, symptoms of outflow obstruction (nocturia, urinary frequency, and terminal dribbling of urine on micturition), or of prostatitis (i.e., perineal pain or discomfort). The gloved and lubricated index finger should be used to palpate the prostate anteriorly. A normal prostate has a diameter of approximately 4 cm, a rubbery consistency, and both lobes and the dividing median sulcus are palpable. An enlarged prostate may result from benign prostatic hypertrophy, malignancy, calculi, or chronic prostatitis. Tenderness of the prostate gland suggests prostatitis; this may be exquisite in acute prostatitis, due, for example, to gonorrhea. It should also be possible to feel the seminal vesicles, which are lateral to the prostate and extend superiorly. These may be abnormally enlarged in certain rare conditions, for example, tuberculous involvement. A rectal mass, likely to be malignant, may also be palpated with the finger. Proctoscopy with a well-lubricated instrument should be carried out if there are symptoms suggestive of proctitis (i.e., rectal discharge, tenesmus, or pain on defecation). The rectal mucosa should be examined visually through the instrument for the presence of erythema, discharge, and condylomata acuminata. If rectal samples are to be sent for microbiological investigation they should be obtained at this stage. Remember that digital and proctoscopic rectal examinations may not be possible in the presence of painful perianal lesions, such as thrombosed external hemorrhoids or herpetic ulceration.

## Examination of Female Patient

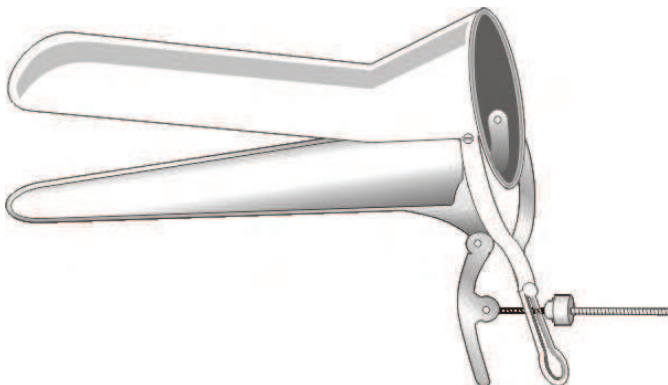
### EXTERNAL GENITAL EXAMINATION

This is best carried out with the patient in the dorsal lithotomy position. Careful inspection of the vulval and perivulval areas should be done. This will necessitate separating the labia majora using both hands, to allow visualization of the labia minora and the urethral meatus. Make careful note of any abnormal findings,

for example, enlargement of Bartholin's gland, condylomata acuminata, urethral discharge (pressure under the urethra with one finger may cause discharge to appear from the meatus), urethral caruncle, paraurethral abscess, vaginal prolapse, or lymphedema. Also separate the buttocks with both hands to allow examination of the perianal area and perineum. Later it may be necessary to examine the patient in the left lateral position to visualize the natal cleft.

### INTERNAL GENITAL EXAMINATION

A bi-valved, self-retaining speculum is preferred (Fig. 24.1). The examination can be rendered less uncomfortable for the patient if a metal speculum is pre-warmed by immersing it in warm water immediately prior to the examination. The labia majora should be separated with the fingers of one hand, and the speculum, in its closed position, slowly and gently inserted into the vagina to its full extent using the other hand. Once fully inserted the blades of the speculum should be gently opened, and in most cases the cervix will be visualized when this is done. If the cervix does not appear, then it may do so if the woman is asked to raise her buttocks off the couch temporarily. If this maneuver fails, then withdraw the speculum and perform a digital examination of the vagina with the lubricated and gloved index finger to locate the exact position of the cervix. Then re-insert the speculum in this direction. It may occasionally be necessary to use an extra-long speculum if the cervix cannot be reached with one of normal size. The cervix and vagina should be carefully inspected for normal features of note (e.g., retention cysts or Nabothian follicles on the cervix) and abnormalities, (e.g., condylomata, the 'strawberry cervix' of trichomoniasis, cervical mass, or ulceration). The consistency, color, and amount of any visible vaginal discharge should be noted. If required, vaginal and cervical samples for laboratory investigation should be obtained at this stage. Similarly, samples can be obtained from the endocervical canal after wiping the cervix with a cotton wool swab or ball to remove adherent vaginal secretions. The speculum should then



**Fig. 24.1:** A bi-valved, self-retaining speculum for internal genital examination in a female patient.

be removed with the blades in a nearly closed position. Be careful not to allow the blades to snap together, pinching the vaginal wall between them, as the instrument is removed. Any urethral samples for microbiological tests should be obtained at this stage. Consideration should be given to performing a bimanual pelvic examination. This is unnecessary if the woman complains of no upper genital tract symptoms. If it is indicated, then the lubricated index and middle fingers of a gloved hand should be inserted into the vagina, whilst the flat of the other hand should be placed on the woman's lower abdomen. Gently but firmly try to approximate the fingers of the two hands in order to palpate the pelvic structures between them; firstly in the midline to palpate the uterus, and then to either side to palpate the ovaries and adnexae (Fallopian tubes and associated ligaments). Do not exert such pressure as to cause the woman any pain. Take note of any abnormal enlargement of the pelvic organs, masses, unusual tenderness, or cervical excitation (i.e., unusual tenderness on gently moving the cervix with the index finger of the examining hand).

### EXAMINATION OF ANOURECTUM

Please refer to the section on the anorectal examination in male patients. Much the same considerations apply in females. A digital rectal examination is rarely indicated in a female patient attending for an STI screen, although it should be carried out if there are symptoms of gastrointestinal blood loss or altered bowel habit. Rectal samples to be tested for gonorrhea and/or chlamydia should be obtained in women who have practiced recent unprotected anal intercourse, and in those who are contacts of known gonorrhea, even if they have not practiced anal intercourse with that partner. These samples can be obtained by proctoscopy, or alternatively by blindly inserting a moistened cotton wool tipped swab through the anus.

### EXAMINATION OF MOUTH AND OROPHARYNX

This is not required routinely but should be done if the person complains of symptoms relating to the area, or if it is clinically indicated for another reason, for example, if the history suggests the possibility of syphilis or HIV infection.

A good light source is essential, and it must be possible to direct this into all parts of the oral cavity (a pen torch is very useful for this purpose). Carefully inspect in turn: the lips, gums, roof, and floor of the mouth, both surfaces, and the sides of the tongue. Look for leukoplakia, ulceration, nodules, and candidiasis.

To examine the oropharynx, ask the patient to open their mouth and to say "eh" or "ah," or to yawn, while holding the tongue down with a tongue blade. This is also the time to take a pharyngeal sample for microbiological testing if indicated (e.g., for gonorrhea in an individual giving a history of receptive fellatio), by quickly sweeping a swab around the oropharynx and tonsillar areas.



## Conclusion

Once the examination has been completed and all necessary samples obtained, the patient should be allowed to dress in privacy. Before they leave the clinic the examining physician should speak to them to discuss the findings, the possible diagnoses and their management, and to arrange follow-up.

In conclusion, the history taking, physical examination, and obtaining of specimens for laboratory investigations are the essential elements in making the diagnosis in a patient with possible STI. It is therefore important that the practitioner establish an efficient routine for carrying them out. On this will also rest the ability to form a satisfactory doctor-patient relationship without which management will fall short of optimal. This is even more true in this field of medicine than others, due to the feelings of shame and embarrassment that many patients will bring to such a consultation, which it is the duty of the physician to dispel through the application of his specialist knowledge, skills, and experience.

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# Genital Mucosal Immunity Against Sexually Transmitted Infections

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## Introduction

The mucosal immune system is an integral part of the whole-body immune system and serves as first line of defense against pathogens transmitted via the respiratory, gastrointestinal, and genital routes. The investigations pertaining to mucosal immunity were hampered in the past by difficulty in isolating and characterizing mucosal associated lymphoid cells and measurement of secretory antibodies from various mucosal-associated tissues at the local site. Better understanding of the genital mucosal immune system is of paramount importance, as occurrence of sexually transmitted infections (STIs) is unabated. It has become even more critical to delineate the immune mechanisms occurring at the mucosal surface of the genital tract in light of the fact that 80–90% of persons infected with human immunodeficiency virus (HIV) acquire the infection through the sexual route.

Protection against STIs is derived either by innate or adaptive immune responses. The adaptive immune response is elicited against particular pathogens by the production of antibodies and/or cell-mediated immune response. Unlike the innate immune response, the adaptive immune response usually confers life-long protection to re-infection by the same pathogen. The adaptive immune system consists of two compartments, the systemic and the mucosal compartment, that are functionally independent.<sup>1</sup> The systemic compartment is represented by the bone marrow, spleen, and lymph nodes whereas the lymphoid tissues in the mucosa and the external secretory glands comprise the mucosal immune system. The mucosal immune system can be divided into discrete inductive (nasal associated lymphoid tissues [NALT], gut associated lymphoid tissues [GALT], and rectal associated lymphoid tissues [RALT]) and effector sites. The Peyer patches (PP), appendix, and smaller lymphoid aggregates called solitary lymph nodes appear to be the major inductive sites in GALT.

The commitment of B cells to form immunoglobulin-A (IgA), the major isotype of the mucosal immune system, is thought to occur in these inductive sites before enteric exposure to an antigen. The noninflammatory nature of IgA is probably of considerable importance for the maintenance of the structural

and functional integrity of mucosal tissues.<sup>2</sup> On encountering the antigen, B cells undergo expansion and differentiate into IgA plasma cells and memory cells. Following the migration of B cells to mucosal effector tissues, such as the lamina propria, and the epithelium of the intestine, upper respiratory, and genitourinary tracts, B cells develop into IgA plasma cells. The differentiation of B cells is facilitated by the presence of antigen specific T-helper (Th) cells as well as cytotoxic CD8+ T lymphocytes along with cytokines. Both CD8+ and Th cells also migrate along with the B cells from the inductive sites to the mucosal effector sites, the route constituting the common mucosal immune system.<sup>3</sup> The epithelial cells that cover the vast surface area of mucosal membranes integrally participate in mucosal immunity not only as mechanical barriers but also as active producers of innate immune factors (e.g., lysozyme, lactoferrin, peroxidase, defensins, complement components, and numerous cytokines). These cells are also involved in the transport of antibodies and act as antigen-processing and presenting cells.<sup>4</sup>

The immune system in the genital tract represents a component of the common mucosal immune system. However, the immune system of the genital tract is the least understood part of the mucosal immune system with respect to the origin of its immune cells, the role of cytotoxic T lymphocyte (CTL) responses, induction of antibody responses and the contribution of serum derived versus mucosally produced antibodies.<sup>3</sup>

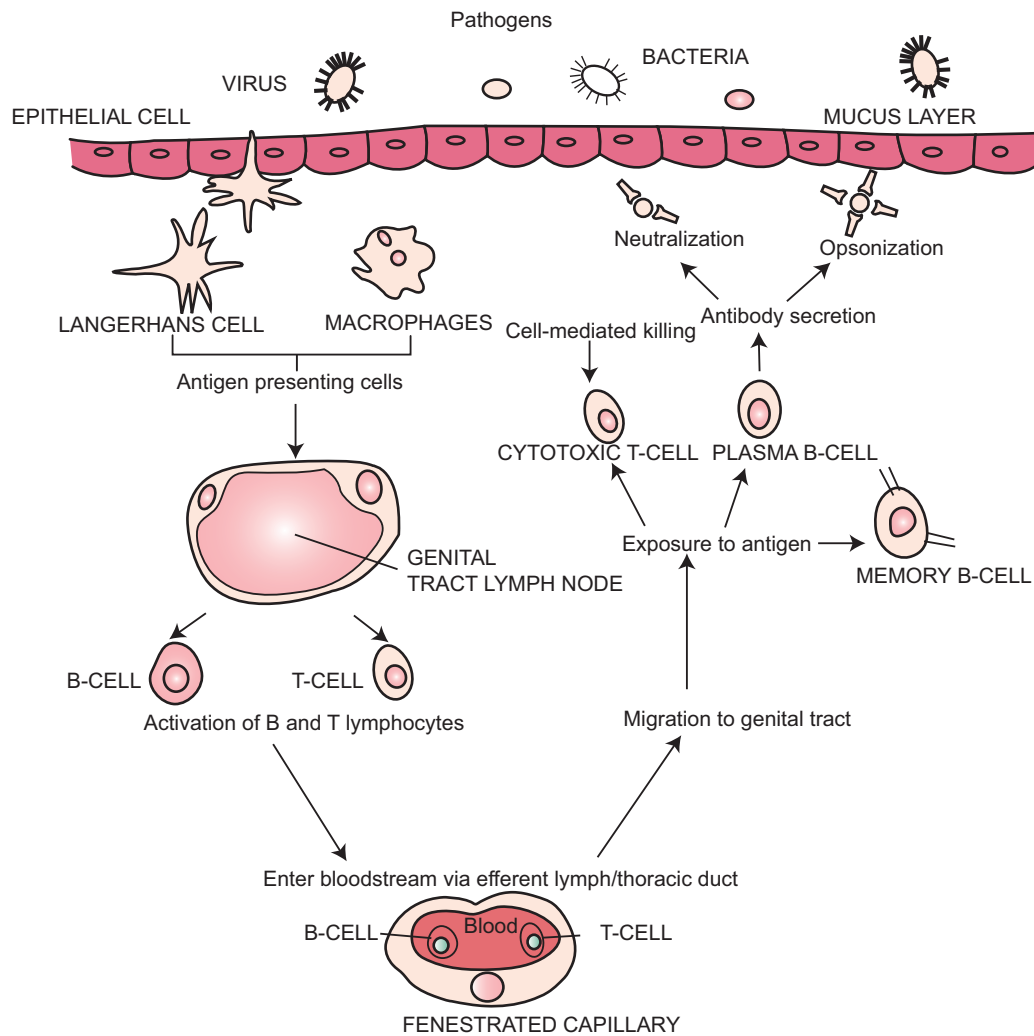
## Female Genital Mucosal Immune System

The mucosal lining of the lower reproductive tract (vagina, ectocervix) is composed of multilayered stratified squamous epithelium whereas the upper reproductive tract (endocervix, endometrium) is composed of a single layer of columnar epithelium. The transformation zone between ectocervix and endocervix where the squamous epithelium abruptly changes to the single layer of columnar epithelium is more vulnerable to infection. Increased numbers of activated lymphocytes and lymphoid aggregates are present in the transformation zone in the presence of various pathogens.<sup>5</sup> Sexually transmitted viruses have to cross the female

genital tract epithelium to manifest infection in the host. Herpes simplex virus type 2 (HSV-2) directly infects genital epithelium and undergoes replication in it.<sup>6</sup> Sex steroid hormones modulate HSV-2 transmission and estradiol provides a protective effect.<sup>6</sup> The interaction of HIV with the genital epithelium is still not completely understood.<sup>7,8</sup> There are contradictory reports with respect to the infection of genital epithelium per se with HIV which may involve alternate cellular receptors such as GalCer, DC-SIGN, mannose receptors, heparin sulfate, and Syndecan.<sup>7-12</sup> Stages of the menstrual cycle and oral contraceptives have been shown to influence susceptibility to candidiasis, gonorrhea, HSV-2, HIV-1, and chlamydia in women.<sup>13,14</sup>

The mechanism of antigen uptake and processing in the female reproductive tract is analogous to a primary immune response in the GALT (Fig. 25.1). Antigens reaching the sub-mucosa of the vagina are taken up by antigen presenting cells (APCs), which then

migrate to the draining lymph nodes. In the female genital tract, Langerhans cells and mononuclear phagocytes present in the vagina are capable of acting as APCs. In mice, antigen absorption in the vagina occurs via Langerhans cells which are MHC class II+.<sup>15</sup> Once in the lymph nodes, the APCs stimulate B and T lymphocytes, including memory sub-populations, which enter the blood stream via the efferent lymph and the thoracic duct. These sensitized B and T lymphocytes migrate to the genital tract and on exposure to the antigen, participate in a secondary immune response.<sup>3</sup> Pathogens adapted to infect mucosa express virulence factors that allow them to adhere, colonize, or invade the epithelium. Secretory IgA (sIgA) prevents adsorption of these viruses, bacteria, and toxins by blocking their adhesion while they are on the external side of the epithelial barrier. By preventing cellular attachment of the antigen, IgA enables it to be flushed away in the stream of secreted fluids and mucous washing over the epithelia.



**Fig. 25.1:** Mucosal adaptive immune system of the female genital tract. Presence of a thick mucus layer in the female genital tract presents the first line of defense against pathogens. Antigen presenting cells (APCs) such as Langerhans cells and macrophages capture antigen and present the antigen to the immune cells in the draining lymph nodes. Activated B and T cells migrate to genital tract where exposure to antigen may lead to secondary immune response as well as generation of memory cells. Activated T cells are responsible for cell-mediated immunity, whereas activated B cells secrete antibodies leading to neutralization/opsonization of pathogens.

The types of immunoglobulins secreted in the female genital tract have been studied in secretions from the fallopian tube, uterus, peritoneal cavity, and in the cervical mucus or vaginal fluid. The hallmark of the mucosal immune system is the production of sIgA.<sup>3</sup> The presence of sIgA has been detected in the secretions of the female genital tract. Using sub-class specific monoclonal antibodies, equal proportions of IgA1 and IgA2 have been detected. Furthermore, in female genital tract secretions, IgA is represented by sIgA, polymeric IgA (pIgA), and monomeric IgA (mIgA), with a slight excess of IgA2.<sup>16</sup> Apart from IgA, cervical mucus secretions also show the presence of IgG (from the systemic circulation) in higher concentrations than IgA. The mechanisms involved in the appearance of IgG in cervico-vaginal secretions have not been explicitly elucidated. A 90% reduction in IgA and 50% reduction in IgG concentrations were observed in the mucus of hysterectomized women, providing indirect evidence that IgA is locally produced in the upper reproductive tract.<sup>17</sup> Human cervical mucus from normal women, sampled throughout the menstrual cycle contained albumin: IgG ratios that approximate those in the serum, suggesting that IgG is derived from the blood circulation.<sup>18</sup> Patients with abnormal cytology had higher concentrations of IgG and even more of IgA in the cervical mucus.<sup>19</sup> The cellular origin of Ig isotypes in the reproductive tract secretions have shown that the lamina propria of the endo- and ecto-cervix contains the highest numbers of Ig-producing plasma cells, with significant numbers being present in the fallopian tubes and vagina. Analyses by Flow Cytometry revealed that the reproductive tract tissues contain 6–20% of leukocytes, with the Fallopian tubes and uterus having a higher proportion of leukocytes than the cervix and vagina.<sup>20</sup> Among the leukocytes, T lymphocytes are a major constituent (30–60%). B cells and macrophages are also detected, but only in small numbers.<sup>20</sup> The uterine endometrium of post-menopausal women had fewer leukocytes than the uterine endometrium of pre-menopausal women. In addition, a hormone dependent change in the immune cell population has been observed in the reproductive tract. Sex hormones have a stimulatory effect on the immune function of females which becomes evident after menarche and diminishes after menopause.<sup>21,22</sup> In the human uterus, for example, immunocompetent cells exhibit a cyclic distribution during the menstrual cycle, representing 10–15% of the stroma during follicular phase and 20–25% in the late secretory phase. Immunophenotypic analysis of leukocytes in uterine endometria in hysterectomy specimens has shown the presence of lymphoid aggregates composed of a B lymphocyte core surrounded by numerous T lymphocytes and an outer layer of macrophages. The aggregates are present during the menstrual cycle in pre-menopausal women and are absent in post-menopausal women.<sup>22</sup> Increased numbers of plasma cells (especially IgA plasma cells) in the submucosa of the endocervix of women with a variety of STIs have also been detected.<sup>23</sup>

Innate immunity in the female reproductive tract utilizes a spectrum of molecules to confer protection against potential pathogens. Among the epithelial cell secretions, soluble factors

with known bactericidal effects are defensins, secretory leukocyte protease inhibitor, lysozyme, lactoferrin, and zinc, as well as other antimicrobial peptides.<sup>24</sup> Natural killer (NK) cells present in the female reproductive tract enhance innate immunity and play an important role in killing hazardous pathogens and tumor cells. The number of NK cells as a percentage of leukocytes in different regions of the female reproductive tract varies between 10% and 30% in non-pregnant women.<sup>20</sup> The differential expression of surface receptors by decidual NK cells may have a role in determining reproductive success through modulation of the maternal immune system at the time of implantation and placentation.<sup>25</sup> Decidual NK cells produce cytokines spontaneously and hence are able to amplify an inflammatory response and promote macrophage activation, endometrial angiogenesis, and generation of cytotoxic T cells.<sup>26,27</sup> Resting uterine NK cells express several toll-like receptors (TLRs), in particular TLR2, TLR3, and TLR4. It has been reported that activation of NK cells via TLR2 leads to release of  $\alpha$ -defensins that can be directly harmful to microorganisms.<sup>28</sup> NK cells have been established as an important effector of innate immunity for a variety of viral infections. In HIV-1 infection in humans, alterations of NK cell function, frequency, and expression of various NK receptors have been reported to be associated with differential dynamics of disease progression.<sup>29</sup> A depressed level of NK activity is one of the various immunological abnormalities observed during HIV infection.

Commensals which normally colonize the mucosa play a significant role in vaginal defense; these include *Lactobacillus* spp., *Staphylococci*, *Enterococcus* spp., *Gardnerella vaginalis*, *Ureaplasma urealyticum*, and *E. coli*. The lactobacilli metabolize glycogen released by vaginal epithelial cells to lactic acid resulting in a low vaginal pH (3.5–5.0) and thus create an acidic environment. Some species of lactobacilli also produce hydrogen peroxide, which is antimicrobial at a concentration of 0.75–5.0  $\mu$ g/ml. These levels of hydrogen peroxide are achievable in the vagina.<sup>30</sup> Keeping this in view, “probiotics” have also been proposed to combat STIs.

## Male Genital Mucosal Immune System

The male lower urogenital tract is exposed to sexually transmitted pathogens and is therefore a strategic site of immune defense. Immunologically, the penile foreskin is characterized by the presence of few T lymphocytes and macrophages. Numerous Langerhans cells, however, are found within the epithelium. The most abundant immune cells of the penile urethra are macrophages. In young adults, virgin male mice, these were found primarily underlying the urethral epithelium, but in older, mated mice, they were usually intraepithelial in location, and were more abundant. Langerhans cells could not be specifically identified in the urethral mucosa. T lymphocytes were found underlying and occasionally within the epithelium of the urethral mucosa, with CD4+ cells more abundant than CD8+ cells. The presence of ovalbumin specific IgA was observed in the urethral mucosa of rats when primed intraperitoneally with ovalbumin followed by intraduodenal plus intraurethral boosting.<sup>31</sup> Murine penile

urethral epithelium expresses secretory components, but few IgA producing plasma cells have been documented.<sup>32</sup> In primates, immunization targeting genital, urinary, and rectal associated lymphoid tissues produced specific IgA antibody titers in urethral secretions and seminal fluid.<sup>33</sup> In the male genital tract secretions, IgG, IgA, and IgM have been detected. In contrast to saliva, milk, and intestinal fluid, in which sIgA is by far the dominant isotype, seminal plasma contains IgG as the dominant isotype and IgM is present at low levels. IgA is represented by sIgA, pIgA, and mIgA, and all three molecular forms of IgA are present in comparable quantities. The levels of these antibodies show variation due to differences in collection procedures, methods, and standards used in immunoglobulin measurements, and the presence of proteolytic enzymes that are essential in semen liquefaction but also degrade immunoglobulins.<sup>34</sup> Parallel measurement of plasma-derived proteins and immunoglobulins in split ejaculates showed that IgG is derived from circulation, while sIgA is of local origin.<sup>35</sup> Detailed analyses of various types of antibodies and their sub-types suggest that humoral immunity in male genital tract is contributed to by both systemic as well as mucosal immune responses.<sup>36</sup> The presence of all the components required to mount a secretory mucosal immune response have been detected in the human penile urethra. IgA and IgM producing plasma cells have been detected along the length of the urethra. Antigen presenting cells have also been detected in the human penile urethra, suggesting that immunity may be induced in this region.<sup>35–37</sup> Recirculating lymphocytes from the thoracic duct entered the male genital organs with a similar distribution to the pattern of lymphoid blasts. There is probably an exchange between these immigrating lymphocytes and the different subsets, which are localized in the epithelium (T suppressor) and interstitial tissue (T helper) in male genital organs. The lymphoid cells in the male genital tract might play an important role in the immune function of seminal fluid and in sexually transmissible diseases. The presence in human seminal plasma of sIgA-associated antibodies to *S. mutans* and the influenza virus, as well as Salmonella-specific antibodies induced by oral immunization, suggests that the male genital tract is also a component of the common mucosal immune system.<sup>38</sup>

### Characteristic Features of the Genital Tract Immune System

The reproductive tracts (male and female) represent components of the common mucosal immune system with unique features which are distinct from other mucosal tissues. The majority of lymphocytes observed around the urethra are positive for the integrin beta 7 alpha M290, which is selectively expressed by mucosal lymphocytes, providing indirect evidence that the urethra is part of the common mucosal system.<sup>37</sup> On the other hand, both male and female genital tracts lack organized lymphoepithelial structures resembling intestinal PPs where mucosal immune responses are induced and transported to remote effector sites.<sup>39</sup> In contrast to GALT, within the uterine epithelium a hormone dependent lymphoid aggregation consisting of B cells, CD8+ T cells, and macrophages has been seen.<sup>3</sup> The

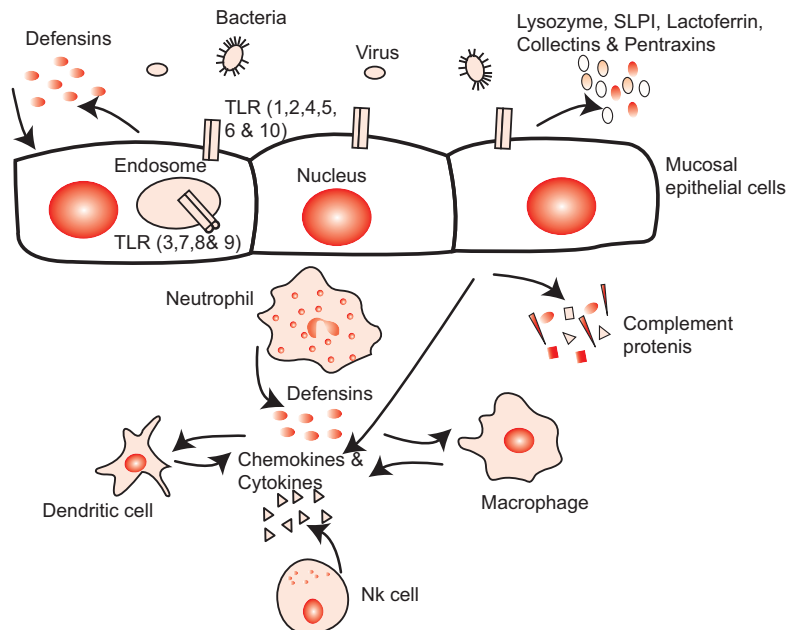
uterine mucosa is transformed from endometrium to decidua during pregnancy and this process is characterized by the presence of a large number of uterine NK cells that are distinct from most NK cells in the peripheral circulation.<sup>40</sup> Immunochemical analysis of female and male genital tract secretions have demonstrated that these fluids display several features that are distinct from other secretions. IgG predominates as compared to IgA both in male and female genital tract secretions, whereas IgA predominates in the gut-associated immune response.

### Characterization of Genital Tract Immune Response to Commonly Occurring STIs

Innate immunity plays a crucial role in combating STIs. The components of cellular immunity of the innate immune response include activated macrophages and NK cells. The components of humoral immunity of the innate immune response include members of the complement cascade and soluble pattern-recognition receptors, such as collectins, ficolins, and pentraxins.<sup>41</sup> These molecules represent functional ancestors of antibodies and play a key role as effectors and modulators of innate resistance in animals and humans as shown in Fig.25.2. Pentraxins are a superfamily of conserved proteins characterized by cyclic multimeric structure and presence of conserved “pentraxin domain” and “pentraxin signature.” The C-reactive protein and serum amyloid P components constitute the short pentraxin arm of the superfamily and play an important role in providing innate resistance to microbes.<sup>42</sup> PTX3 is a prototype long pentraxin produced by cells involved in innate immunity and by other peripheral tissues. PTX3 binds specific pathogens, such as fungi, bacteria, and viruses, promoting phagocytosis and consequent clearance of the pathogen.<sup>43,44</sup> Surfactant protein A, a member of collectin family of proteins is expressed in the vagina, has the ability to facilitate phagocytosis of microorganisms, stimulate chemotaxis, increase the oxidative burst by phagocytes, and modulate proinflammatory cytokine production by immune cells.<sup>45</sup>

Innate immunity depends on detection of the constituents of pathogens by the TLR family. To date, 10 TLRs (TLR1–10) in humans and 12 TLRs (TLR1–9 and TLR11–13) in mice have been found. Although present in mice, the human TLR11 gene appears to contain a stop codon that would prevent its expression. TLRs recognize pathogens through evolutionary conserved pathogen-associated-molecular-patterns such as lipopolysaccharides, peptidoglycan, flagellin, double-stranded RNA, and bacterial CpG DNA. Recognition of pathogen-associated-molecular-patterns by TLR leads to activation of NF- $\kappa$ B followed by an increased secretion of proinflammatory cytokines such as IL-6, IL-8, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) leading to killing and clearance of pathogen.<sup>46</sup> Expression of TLR1 to TLR11 in addition to other signaling components such as CD14 and MyD88 have been observed in the male urogenital tract.<sup>47</sup> Activation of TLRs by using various TLR ligands such as CpGA (TLR-9 ligand), poly I:C (TLR-3 ligand), and flagellin (TLR-5 ligand) have been shown to reduce viral infections.<sup>48–50</sup>





**Fig. 25.2:** Mucosal innate immune system in the reproductive tract. The innate immune system provides the first line of defense against a wide range of microorganisms before the development of adaptive immune response. Epithelial cells, and neutrophils secrete molecules like defensins, secretory leukocyte protease inhibitor, lysozyme, lactoferrin, pentraxins, and collectins, which have anti-microbial activity and play a key role as effectors and modulators of innate immune response. Activated macrophages, dendritic cells, and natural killer cells, in turn secrete chemokines, cytokines and components of complement system. Toll like receptors expressed by various reproductive tract associated cells recognize conserved sequences called pathogen-associated-molecular-patterns present on bacteria, viruses, and fungi and hence help in their elimination.

In the intestinal tract, the mucosal immune response is frequently initiated by antigen uptake by microfold (M) cells which overlay the PPs. Since M cells have not been described in the vagina or cervix, it was suggested that the genital mucosa is a poor site for induction of mucosal immune responses. Consequently, local humoral and cellular immune responses stimulated by infections such as *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, papillomavirus, and HIV-1 are weak or absent, and repeated local intravaginal immunizations result in minimal humoral responses. Because a significant proportion of IgG in genital tract secretions is derived from the circulation, systemic immunization may provide protective IgG antibody-mediated immunity in the genital tract. The female reproductive tract, depending upon its ability to mount an immune response, can be divided into non-sterile and sterile regions. The non-sterile regions include vagina and ectocervix while the sterile region comprises of endometrium, fallopian tube, and endocervix.<sup>30</sup> Assessment of immunoglobulins produced against STIs has shown that the response generated in the mucosal tract of infected persons is comparable to that in uninfected individuals. For example, women diagnosed with gonococcal cervicitis showed low local mucosal IgA and IgG against *Neisseria gonorrhoeae* whether measured in cervical mucus, vaginal washes, serum, or saliva. This showed little or no significant difference from antibodies measured in individuals from the same population who were not infected with *N. gonorrhoeae*. In men with gonococcal urethritis, low levels of antigenococcal IgG and IgA were found and these were not

significantly different when compared to uninfected subjects.<sup>51,52</sup> The poor response to *N. gonorrhoeae* infection is due to the ability of the pathogen to protect itself against the immune response by several mechanisms like extensive and rapid antigenic variation of surface proteins, variation and sialylation of lipopolysaccharides, interference with complement mediated lysis, and the production of IgA1 protease.<sup>51</sup> In the case of HIV, the immune system is not able to mount a response against the virus due to the ability of the virus to evade the immune system by frequent mutations. The antibodies produced against a particular strain become ineffective in preventing infection with another strain. The virus is able to replicate within human cells by binding a human cellular protein (cyclophilin) to its capsid, which blocks the action of the inhibitor restriction factor-1. Within monkey cells, the virus is not able to replicate itself due to the binding of the inhibitor to the capsid of the virus.<sup>53</sup> The limited ability of the reproductive tract to mount an immune response, along with the ability of some of the pathogens to evade the immune system, suggests a need to enhance the mucosal immune response to counter STIs.

### Strategies for Enhancing Mucosal Immune Responses against STIs

The absence of an effective vaccine for the prevention of AIDS and most other STIs has generated renewed interest in augmenting the immune response in the reproductive tract to combat these infections. Vaccination via a mucosal route is a

very attractive option for immunization, because both local and systemic immune responses are inducible and vaccines can be administered easily and safely from infants to elderly persons. Since the genital mucosa is usually the major entry for sexually transmitted pathogens, the focus has been on priming the genital mucosal tract to prevent the infections. In order to generate adequate mucosal immune response against STIs, different strategies like immunization with whole pathogen (live-attenuated or killed) or the use of antigenic epitopes of the infectious agents (protein/protein subunit, polysaccharide, or polysaccharide-protein conjugate) have been adopted.<sup>54</sup> Topical microbicides, self-administered agents designed for vaginal use that block transmission at the mucosal surface, may provide a realistic method of intervention. In addition, different routes of immunization (systemic, oral, rectal, vaginal, tracheal, or nasal) have also been tested to obtain an optimal response.

## IMMUNOGENS

### Whole Pathogen

#### Killed

Killed pathogens have been used as immunogens to prevent STIs and have proved to be successful against other diseases like influenza, polio, typhoid, etc. Many of these vaccines have already been overtaken by new and improved versions, including subunit vaccines and orally active preparations. The use of heat-killed chlamydia was unable to elicit a sufficient immune response to prevent infection. This may be due to the inability of the inactivated organisms to mobilize mature dendritic cells.<sup>55,56</sup> Intrarectal administration of heat killed *Candida albicans* in combination with a mucosal adjuvant LT (R192G), a genetically detoxified form of the heat-labile toxin of enterotoxigenic *Escherichia coli*, in male mice produced anti-*C. albicans* antibodies. These animals were able to eradicate intravenous challenge with *C. albicans* better than the animals immunized with heat-killed *C. albicans* alone.<sup>57</sup>

The use of whole inactivated virus as immunogen has been one of the strategies adopted to develop vaccines against HIV. Initial experiments in macaques with whole killed simian immunodeficiency virus induced sterilizing immunity against the virus.<sup>58</sup> However, subsequently it was observed that the protective immunity observed in these animals was contributed to, at least in part, by the immune response against human cellular antigens.<sup>59</sup>

#### Live Attenuated

Immunogens used in this form are the most successful vaccines currently in use. Many viral vaccines of this type have an efficacy of more than 90%, and protection frequently lasts for many years. Their ability to replicate enables them to induce a full range of immune response including an MHC-class I restricted cellular response. The use of live-attenuated lentivirus “vaccines” has shown best protection from uncontrolled viral replication and

clinical disease after pathogenic simian immunodeficiency virus challenge.<sup>60</sup> However, various safety concerns have prevented the use of such immunogens, primarily due to the fear of reversion to the wild active type.

## Subunit Vaccines

The drawback in using the whole pathogen for generating protective immunity is that the immune response generated is non-specific and this may have adverse effects on the health of the infected person. Hence, the concept of developing subunit vaccines was explored. Intradermal immunization with *Candida albicans* recombinant heat shock protein 90 kDa (hsp90-CA) followed by intranasal or intradermal boosting induced a significant increase in both serum and vaginal hsp90-CA-specific IgG and IgA antibodies. In the intradermally boosted group, subsequent experimental vaginal *Candida* infection induced an additional increase in the hsp90-CA specific IgG isotype, suggesting that specific antibody responses may be generated during vulvovaginal candidiasis.<sup>61</sup> Trichomonads can cause both human and bovine infection. The causative organism in cattle is *Trichomonas foetus*. Immunization of cattle with a surface antigen (TF1.17) provided protection against trichomoniasis.<sup>62</sup> Immunization of rabbits with recombinant *T. pallidum* repeat protein *K* (*TprK*) showed that the lesions developed were smaller, did not ulcerate or have detectable treponemes, and healed more rapidly than the lesions in control rabbits.<sup>63</sup> Further studies using fragments of *TprK* in rabbits showed that of the three fragments tested, fragment 1 (amino acids 37–273) was the most effective in preventing ulceration of lesions. Fragment 3 (amino acids 349–478) had intermediate effects, whereas fragment 2 (amino acids 274–348) was ineffective. These results demonstrate that epitopes in fragment 1 are recognized by T cells, and antibodies are produced during infection. Immunization with this portion of *TprK* therefore most effectively attenuates the development of syphilitic lesions.<sup>64</sup> Conceptually, subunit vaccines should be effective in generating specific immune responses and thereby provide long-lasting protective immunity. In practice though, no single subunit vaccine has yet produced a sterilizing, long-term immunity. The induction of a high level of Th-1 response along with a substantial IgA and IgG antibody response at the mucosal site of infection is a prerequisite for developing protective immunity. This makes the development of a multi-subunit vaccine approach more plausible than the single subunit vaccine approach. Researchers at Antex Biologics (Maryland, USA) are developing TRACVAX, a multi-subunit vaccine based on recombinant subunits of proteins from *Chlamydia trachomatis*.<sup>65</sup> The exact antigen composition of this vaccine is not known, but it is likely to feature chlamydial proteins from a super family known as polymorphic membrane proteins.<sup>65</sup> A further study examined a vaccine composed of a combination of the major outer membrane protein and porin B protein of *C. trachomatis* that have a protective advantage over a single subunit construct. The results showed that significant levels of chlamydia-specific sIgA and IgG2a were detected in vaginal washes and serum of immunized mice, and the multi-subunit

construct induced a significantly higher level of Th1 response than the single subunits as measured by the amount of interferon-gamma produced by immune T cells in response to re-stimulation with ultraviolet-irradiated elementary bodies *in vitro*.<sup>66</sup>

The simultaneous expression of structural proteins of virus can produce virus-like particles (VLPs) by a self-assembly process in a viral life cycle even in the absence of genomic material. Taking advantage of structural and morphological similarities of VLPs to native virions, VLPs have been suggested as a promising platform for new viral vaccines. In order to develop a vaccine for prevention of HPV infection which has implications in the reduction of cervical cancer, it was demonstrated that HPV-16 L1 capsid proteins form highly immunogenic VLPs.<sup>67</sup> Subsequently, scientific efforts from various groups led to the development of prophylactic vaccines composed of self-assembled VLPs of L1 major capsid proteins that are currently in the market: Gardasil (Merck) and Cervarix (GlaxoSmithKline).<sup>68</sup> Cervarix is designed to protect from infection with HPV-16 and HPV-18, which cause 70% of cervical cancer whereas Gardasil, in addition to these also prevent infection from HPV-6 and HPV-11 which cause 90% of external genital warts. Gardasil contains only aluminum hydroxide as adjuvant whereas Cervarix has AS04, which is comprised of monophosphoryl lipid A (MPL), a detoxified form of lipopolysaccharide and aluminum hydroxide. Aluminum salt based adjuvants typically induce Th2 type response, which is important for a VLP based vaccine system. However, MPL activates innate immune responses via TLR molecules and hence can induce a mixed Th1/Th2 differentiation pattern in human T cells.<sup>67</sup> Recently, vaccinations using these VLPs through nasal and oral routes suggested that these may be antigenically stable and provide the possibility of vaccinating large populations with HPV VLPs without using syringes.<sup>69</sup>

Cellular immune response appears to be the key component necessary for clearance of HPV infections and therefore would be the main target of any therapeutic HPV vaccine. HPV therapeutic vaccines focus mainly on E6 and E7 proteins. Several studies have shown that immunotherapy targeting E6 and/or E7 using vaccinia vectors generates strong cytotoxic T-lymphocyte activity and antitumor responses in preclinical studies.<sup>70</sup> In addition, attenuated *Salmonella* and *Bacillus Calmette-Guerin* have also been proposed as safe and immunogenic to develop bacterial vectors for vaccines encoding HPV-16 L1 and E7.<sup>69,71</sup>

## Polysaccharide

Over the last 20 years protein-polysaccharide conjugate vaccines have been developed to protect against the major invasive bacterial diseases of childhood, *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib), and *Neisseria meningitidis*. These vaccines induce a protective immune response to capsulated bacteria that infect the blood stream. This approach has also been tried for the development of vaccines against STD pathogens. A vaccine composed of liposome-mannan complexes of *C. albicans* produced protective antibodies against disseminated candidiasis.<sup>72</sup> A further study showed that immunization of mice with MAb 6.1, a monoclonal antibody specific for b-1, 2-mannotriose in the mannan complex, protected

mice against infection with *C. albicans*, when administered both intravaginally and intraperitoneally.<sup>73</sup>

## Peptide Vaccines

Peptide vaccines can be synthetically prepared and generally include multiple epitopes corresponding to different proteins of a pathogen. The approach can also deal with serotype variation of antigens, epitopes being chosen from multiple strains. Peptide vaccines suffer from the constraint that many antibodies are directed to conformational determinants. In a study using a combination of T-20 (class 1) and (CCIZN17)(3)(class2) fusion peptides, the result provided evidence that these classes of fusion peptides work synergistically in an *in vitro* infectivity assay in inhibiting the entry of primary HIV-1 isolate 89.6.<sup>74</sup>

## DNA Vaccines

DNA vaccines represent a new approach to the control of infectious disease including STIs. DNA immunization offers many advantages over the traditional forms of vaccination. It is able to induce the expression of antigens that resemble native viral epitopes more closely than standard vaccines do, since live-attenuated and killed vaccines are often altered in their protein structure and antigenicity. Plasmid vectors can be constructed and produced quickly and the coding sequence can be manipulated in many ways. DNA vaccines encoding several antigens or proteins can be delivered to the host in a single dose, only requiring a microgram of plasmids to induce immune responses. Rapid and large-scale production is available at costs considerably lower than traditional vaccines, and they are also temperature-stable making storage and transport much easier. Another important advantage of DNA vaccines is their therapeutic potential for ongoing chronic viral infections. DNA vaccination may provide an important tool for stimulating an immune response in HBV, HCV, and HIV patients. The continuous expression of the viral antigen caused by gene vaccination in an environment containing many APCs may promote a successful therapeutic immune response which cannot be obtained by other traditional vaccines.<sup>75</sup>

A variety of DNA prime and recombinant viral boost immunization strategies have been developed to enhance immune responses in humans. The safety and immunogenicity of an HIV vaccine that combines a plasmid-DNA priming vaccine and a modified vaccinia virus Ankara (MVA) boosting vaccine concluded that this HIV-DNA priming-MVA boosting approach is safe and highly immunogenic.<sup>76</sup> A therapeutic DNA vaccine directed to tumor-specific antigens of the HPV can synergistically enhance immune responses for the treatment of cervical cancer.<sup>77</sup> As DCs are the primary mediators of DNA vaccine-induced immune responses, vaccines that modify intracellular or extracellular movement of antigen or other DC properties are able to enhance DNA vaccine potency.<sup>78</sup> Co-administration of E7 containing DNA with DNA encoding antiapoptotic proteins is able to enhance E7-specific immune responses, tumor treatment, and DC survival. To improve delivery and antigenicity of HPV DNA vaccines, the



use of encapsulation of plasmid DNA encoding fragments derived from E6 and E7 of HPV-16 and HPV-18 in biodegradable particles (ZYC101a) has been reported.<sup>79</sup>

## MICROBICIDES

Although immunization to control the spread of STIs would be ideal, there are currently no protective vaccines available against HIV. The clinical trials of the candidate HIV vaccines showed partial protection. Further, drug resistance has been reported for antiretroviral drugs, the only major therapeutic options currently available for treatment of HIV infected subjects. Hence, it is imperative to explore alternate therapeutic options. The development of vaginally/rectally applied topical microbicides that would be effective against a broad range of pathogens has been identified as a high-priority approach to control STIs including HIV. Microbicides are self-administered prophylactic agents that could be applied topically to the vagina or rectum in various formulations, including gels, creams, suppositories, films, or as a sponge or ring that releases the active ingredient over time, and are one of the most promising technologies under development to reduce the risk of contracting STIs including the HIV. They provide excellent potential as a female controlled preventive option which would not require negotiation, consent or even knowledge of the male partner. Microbicides prevent HIV infection by various mechanisms, such as:

- (i) Vaginal defense enhancers, such agents that maintain an acidic pH hostile to HIV. These agents aim to enhance the vaginal natural acidic environment and production of hydrogen peroxide, which are hostile to pathogens. These include BufferGel, Acidform, lime juice, and Lactobacillus. Natural substances such as antimicrobial peptides (gramicidins and magainins), defensins, retrocyclins, bactenecin, and protegrins are other potential compounds that may be developed as vaginal microbicides in the future.<sup>80,81</sup>
- (ii) Non-specific agents, like detergents, disrupt membranes of cell-free HIV as well as infected donor and uninfected host cells. Microbicides in this category include surfactants (Nonoxynol-9, Octoxynol-9, and Mentegol) that disrupt the lipid membrane.
- (iii) Viral membrane binding agents, commonly polyanions that interfere with cell-virus interactions. These microbicides inhibit the attachment of pathogens to the mucosal surface of the target cells. These include sulfated and sulfonated polymers such as Carraguard, PRO-2000, cellulose sulfate. An “invisible condom” (based on a non-toxic polymer-based gel) has also been proposed that also serves as a barrier against viruses and bacteria.
- (iv) Specific host cell binding agents such as CCR5 inhibitors that prevent cell-virus binding with high specificity such as Maraviroc.
- (v) Inhibitors of viral replication such as tenofovir (nucleotide analog) or UC-781 (nonnucleoside reverse transcriptase inhibitor) that act within CD4+ cells to prevent reverse transcriptase activity.

*In vitro* studies of Praneem, an Indian polyherbal microbicide, have shown activity against clinical isolates of *Neisseria gonorrhoeae* and multidrug-resistant *Escherichia coli*.<sup>82</sup> Basant, another Indian polyherbal cream inhibits the growth of WHO strains and clinical isolates of *Neisseria gonorrhoeae*, including those resistant to penicillin, tetracycline, nalidixic acid, and ciprofloxacin, and has pronounced inhibitory action against *Candida glabrata*, *Candida albicans*, and *Candida tropicalis*.<sup>83</sup> It has also displayed virucidal activity against HIV *in vitro*.

There are approximately 60–80 candidate microbicides currently in development. The majority of these have been evaluated using *in vitro* assay systems and some are undergoing preclinical evaluation. Sixteen candidate microbicides have entered the clinical phase of development. Candidate microbicides that have completed efficacy trials such as Carraguard, have failed to prevent HIV infection.<sup>84</sup> Nonoxynol 9 (N9) also showed an increased risk of HIV transmission in the COL-1492 study.<sup>85</sup> The recent disappointing results from the trials of microbicides have prompted a renewed commitment to basic research to develop additional microbicides for more effective prevention of HIV infection and other STIs.

## Routes of Immunization

Immune responses generated against STIs have also been shown to depend on the route of immunization. Exploitation of immunization routes that are effective for induction of mucosal immune responses taking into account our current knowledge of the origin of antibodies and of specific antibody-forming cells in mucosal tissues is likely to reduce the incidence of many sexually transmitted diseases including AIDS. Since the genital mucosa is a component of the common mucosal immune system, various other routes of immunization have been tried apart from immunizing through the genital mucosa. These include oral, systemic, nasal, and recently transcutaneous immunization.<sup>86,87</sup> Transcutaneous immunization induces a mucosal immune response in the female genital tract.<sup>87</sup> Intranasal immunization has been found to give rise to substantial IgA and IgG antibody responses in the human cervico-vaginal mucosae.<sup>88</sup> The rationale for carrying out immunization through different routes was the observation that intraperitoneal immunization of rats with sheep red blood cells induced to IgA and IgG antibodies in the vagina.<sup>89</sup> This observation helps to confirm the presence of a common mucosal immune system, which in an earlier study was shown by an adoptive lymphocyte transfer method.<sup>90</sup> The application of the immunogen through the intranasal route was shown to induce an enhanced immune response in the genital tract. Intranasal immunization of female mice with a recombinant adenovirus vector expressing glycoprotein B (gB) of herpes simplex virus produced secretory and serum derived humoral immune responses in the genital tract. Intranasal immunization induced anti-HSV gB IgA and IgG in vaginal washes of mice, whereas intra-peritoneal immunization induced only IgG, which was serum derived. Intravaginal immunization produced little anti-HSV



gB IgA and only low levels of specific IgG in vaginal washes.<sup>91</sup> Intranasal immunization with glycoprotein 120 depleted HIV-1 immunogen in combination with immunostimulatory CpG oligodeoxynucleotides (ODNs) produced enhanced levels of anti-p24 IgG and IgA antibodies in serum and vaginal washes compared to mice immunized with HIV-1 immunogen alone or with control ODN. Mice immunized intranasally with HIV-1 immunogen plus CpG were protected against intravaginal challenge with a recombinant vaccinia virus expressing HIV-1 gag.<sup>92</sup> Intranasal immunization with a recombinant vaccinia vector capable of expressing glycoprotein D of HSV-1 provided protection against the development of latent trigeminal ganglionic infection when mice were challenged with a sub-lethal dose of HSV by the lip or nasal route.<sup>93</sup> Recombinant adenovirus expressing glycoprotein B of HSV-1, when administered intranasally, provided protection from systemic heterologous challenge.<sup>94</sup> In mice, vaginal application of anti-HSV antibodies prevented infection and visible signs of genital herpes infection at a dose of ~10 ng.<sup>95</sup> In the vaginal epithelium of T lymphocyte depleted mice, HSV-2 infection caused more fulminant infection as compared to the non-depleted ones.<sup>96</sup> A single rectal immunization of female C57Bl/6 mice with live-attenuated herpes simplex virus type 2 lacking thymidine kinase (HSV-2 TK-) was shown to confer HSV-specific cellular and humoral immune responses as well as protection against an otherwise lethal vaginal challenge with a virulent HSV-2 strain. The immunity afforded by rectal immunization with HSV-2 TK- was shown to be independent of sex hormonal influence and the usage of the adaptor protein myeloid differentiation factor 88 (MyD88).<sup>97</sup> Treatment with estradiol of mice immunized with HSV showed better protection and decreased pathology than progesterone-treated group.<sup>98</sup> Female sex hormones not only regulate susceptibility to various STIs but also play an important role in generating protective immunity.

## Strategies to Enhance Mucosal Immune Response

Vaccine delivery is represented by a diverse range of technologies and approaches, which are linked by the objective of improving vaccine performance or potency. Potentially effective delivery vehicles should promote the induction of adequate levels of mucosal T cell and antibody responses that mediate long-term protective immunity. In order to enhance the mucosal immune response, applications of the antigens incorporated in various delivery systems have been tried.<sup>99,100</sup> These include the following:

- (i) **Co-administration of immunogens with adjuvants active at mucosal surfaces** Some non-toxic mutants of the *E. coli* heat-labile enterotoxin (*LTK63*) have been observed to act as strong mucosal adjuvants when administered through intravaginal and intranasal routes in mice. Certain adjuvants, such as cholera toxin and related enterotoxins can promote mucosal cytotoxic T-lymphocytes (CTL) development when administered orally or nasally with soluble proteins and peptides.<sup>101,102</sup>

- (ii) **Coupling immunogens to carrier molecules that promote their uptake at mucosal inductive sites** Mice immunized intranasally with a recombinant chimeric protein consisting of saliva-binding region of *Streptococcus* and A2 & B subunits of cholera toxoid or type II heat labile enterotoxin of *E. coli* elicited a strong serum IgG and IgA response as well as salivary and vaginal responses. It was also observed that the immune response persisted for 1–2 years and could be recalled by booster immunization.<sup>103,104</sup> In another study recombinant influenza A/PR8/34 (H1N1) viruses were generated by insertion of immunodominant T cell epitopes from chlamydial MOMP into the stalk region of the neuraminidase gene. Intranasal immunization of mice with recombinant virus resulted in a strong Th1 response against intact chlamydial elementary bodies. Also, immunized mice enjoyed significant protective immunity by shedding less chlamydia and rapidly clearing the infection. Furthermore, a high frequency of chlamydia-specific Th1 response was measured in the genital mucosa and systemic draining lymphoid tissues within 24 hr after challenge in vaccinated mice.<sup>105</sup>
- (iii) **Expression of antigens in live-attenuated bacterial or viral vectors that can colonize mucosal tissues** Several live vectors of both bacterial and viral origin have been engineered to provide various cytokines to further stimulate or modulate the immune response. Recombinant adenovirus expressing herpes simplex virus glycoprotein B was shown to be an effective vaccine when given intranasally to mice. This induced serum IgG as well as pulmonary IgA anti-glycoprotein B responses and it protected from challenge with the virus.<sup>89,93</sup>
- (iv) **Incorporation of antigens into a variety of microparticulate or adhesive vehicles that are taken up in mucosal inductive sites** Various lipid-based structures with entrapped antigens such as liposomes, immunostimulating complexes, and different types of biodegradable particles based on starch or copolymers of lactic and glycolic acid have been evaluated. In addition, various mucosa-binding proteins, including both classical plant lectins and bacterial proteins such as the binding subunit portions of cholera toxin or *E. coli* heat-labile enterotoxin, to which antigens have been linked either chemically or as gene fusion proteins have been proposed. Protection against *C. albicans* and *C. tropicalis* infection was observed on vaccination with liposome encapsulated *C. albicans* surface mannan.<sup>65</sup> Promising results have recently been reported from the use of so-called pseudoviruses, or VLPs.<sup>67</sup>
- (v) **Targeting lymphocytes induced by the mucosal immune system to the genital tract tissue** The adhesion molecules (addressins) expressed on the endothelium of blood vessels supplying the tissues help in the recruitment of lymphocytes to tissues. These adhesion molecules serve as ligands for the attachment of lymphocytes expressing the receptors that bind to the adhesion molecules. Within the genital tract tissues, the expressed addressins include intercellular adhesion molecule-I

and vascular cell adhesion molecule-I that are known to be specific binding molecules for lymphocytes.<sup>96,106</sup>

## Conclusion

The genital mucosa is the major entry point for various sexually transmitted pathogens. Hence, it is important to bolster mucosa lining the genital tract so as to enable it to combat these infections at the very site of their entry. For this it is important to generate immune responses that can act both locally as well as through the systemic route. One strategy to elicit enhanced genital mucosal immunity can be the use of a multi-subunit vaccine approach. Also, the various routes of application of the immunogen may prove vital in this process. Studies have shown that the nasal route is able to elicit antibodies in the genital tract against various organisms. Apart from the route of application, the conjugation of the immunogen to carrier molecules, like cholera toxin, has shown to induce a better immune response. Another important aspect is to understand the induction of cell-mediated immunity in the genital mucosa, and the mechanism of generation and recall of memory in the mucosal immune system.

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# 26

## Laboratory Diagnosis of Sexually Transmitted Infections

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### Introduction

The continuing epidemic spread of human immunodeficiency virus (HIV) and other sexually transmitted infections (STIs) call for the appropriate management of patients with STIs and their sex partners for the effective prevention of HIV infection. Adequate management of STIs includes an early diagnosis and correct medical treatment, which is dependent on case finding through reliable laboratory procedures.

Laboratory services are important for the development and implementation of STI/HIV control programmes in the following areas: (i) programme management, (ii) patient management, and (iii) research on the development of new diagnostic tests, drugs, and control methodologies. The laboratory plays an essential role in epidemiological and microbiological surveys, antimicrobial susceptibility studies, the validation of treatment, and sexually transmitted diseases (STD) case management approaches such as the syndromic approach.

Though the syndromic approach to STD case management enables healthcare workers to successfully manage more patients with STIs, there are limitations to this approach. There is considerable over treatment, which is clearly preferable and more cost effective than under-treatment for many curable STIs. Nonetheless, the approach can be made more specific by the judicious use of laboratory tests. Besides, tests are essential for the diagnosis of asymptomatic patients, such as for the screening of pregnant women for syphilis and screening of individuals for HIV seropositivity during asymptomatic stage.

In the developing world, laboratory services for STIs are often not available, or not accessible. Despite the existence of national policy for antenatal screening to prevent congenital syphilis, the implementation remains low because of lack of screening tools that can be used in primary healthcare (PHC) settings.<sup>1</sup>

The development of new and rapid nucleic acid amplification tests (NAATs) in the last decade has considerably widened the field of laboratory diagnosis of STIs. Introduction of multiplexing in the new methods has facilitated diagnosing multiple agents by a single test. The tests should be evaluated in field situations

to determine sensitivity and specificity and to make them cost effective, especially in the developing countries. This will offer specific treatment for patients without any delay. In this regard, the World Health Organization (WHO) STD Diagnostics Initiative has developed the ASSURED criteria as a benchmark to decide if tests address disease control needs: Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free, and Deliverable to end-users.<sup>1</sup>

Use of non-invasive methods for collection of specimens, like vaginal tampons and first void urine (FVU) has been found to be extremely useful especially for the screening of asymptomatic low prevalence populations.<sup>2</sup> In 2006, a National Institute for Health Workshop supported the use of self-obtained vaginal swabs (SOVSs) as specimens for diagnosis of STIs. It concluded that SOVSs are well accepted by women of all ages and perform as well as or better than other specimen types for detection of *Chlamydia trachomatis* (*C. trachomatis*) and *Neisseria gonorrhoeae* (*N. gonorrhoeae*) using transcription-mediated amplification methods (TMA).<sup>3</sup>

Table 26.1 describes the various symptoms of STIs, the individual STIs for which laboratory tests are available, and the ideal specimens required. The collection of specimens constitutes a very important pre-requisite for ideal results. The guidelines for the collection and transport<sup>2</sup> of samples are described below and specific techniques noted.

### Guidelines for Collection and Transport of Specimens

The following guidelines should be considered for the collection and transport of specimens:

- There should be close and frequent discussions between the clinicians, public health managers and the laboratory staff members regarding collection, transportation, and testing.
- The laboratory should provide sterile specimen containers/transport media/culture plates (in the case of *N. gonorrhoeae* culture) to the clinic in advance. The use of leak-proof specimen containers and appropriate swabs is recommended.

**Table 26.1:** Appropriate Specimens and Diagnostic Tests for Common Microorganisms Transmitted Through Sexual Route

Symptoms	Etiological Agents	Test(s)	Specimens
Genital ulcers	<i>T. pallidum</i>	Dark field examination Antigen detection PCR Serology	Fluid from ulcer Swab from ulcer Swab from ulcer Blood
	<i>H. ducreyi</i>	Smear from ulcer, culture, PCR	Ulcer swab Ulcer swab/vesicle fluid
	HSV	Smear from ulcer/vesicle Antigen detection, PCR Serology	Ulcer swab Blood
	<i>C. granulomatis</i>	Impression smear	Tissue biopsy
Urethral or cervical discharge	<i>N. gonorrhoeae</i>	Direct smear, culture Antigen detection DNA tests	Discharge/Swab-Urethral/ endocervical/rectal/ pharyngeal, FVU, SOVS
	<i>C. trachomatis</i>	Culture Antigen detection DNA tests	Swab-Urethral/ endocervical FVU, SOVS
	Mycoplasmas	Culture DNA tests	Swab-Urethral/ endocervical, FVU
	<i>T. vaginalis</i>	Direct wet mount Culture, DNA tests	Urethral discharge /swabs, FVU in males
Vaginal discharge	<i>T. vaginalis</i>	Direct wet mount Culture, DNA tests	Discharge /swab/SOVS
	<i>C. albicans</i>	Direct smear Culture and speciation	Discharge /swab/SOVS
	<i>G. vaginalis</i> & other anaerobic organisms	Direct smear	Discharge /swab/SOVS
Asymptomatic	HIV, HBV HCV <i>N. gonorrhoeae</i> <i>C. trachomatis</i> <i>T. pallidum</i> (latent syphilis)	Serology Serology As above As above Serology	Blood Blood As above As above Blood

FVU, first void urine; SOVS, self-obtained vaginal swab; PCR, polymerase chain reaction; *T. pallidum*, *Treponema pallidum*; *H. ducreyi*, *Haemophilus ducreyi*; *C. granulomatis*, *Calymmatobacterium granulomatis*; *N. gonorrhoeae*, *Neisseria gonorrhoeae*; *C. trachomatis*, *Chlamydia trachomatis*; *T. vaginalis*, *Trichomonas vaginalis*; *C. albicans*, *Candida albicans*; *G. vaginalis*, *Gardnerella vaginalis*; HBV, Hepatitis B virus; HCV, Hepatitis C virus.

- The clinicians/paramedics entrusted with the collection of specimens should have adequate knowledge of standard precautions and should practice them to avoid needle prick and exposure to blood/body fluids.
- Contamination from indigenous commensal flora, e.g., skin microbes, should be avoided to ensure representative sampling.
- Adequate volumes of each specimen should be collected.
- Immediately after collection, each specimen should be labeled with the patient's name, identification number, source, the date and time of collection.
- Transport conditions should be optimal as the pathogens responsible for STIs are usually fastidious and fragile. Hence, procedures detecting viable organisms may give false-negative results. In general, the specimens should be transported rapidly for the recovery of infectious organisms, using nutritive and non-nutritive systems and avoiding excesses of temperature, especially when culture is attempted. When tests for detection of antigen/antibodies are used, transport conditions are usually less stringent.

- In case the laboratory is away from the clinic, specimens should be transported in sealable, leak-proof plastic bags, having a separate compartment for proformae. Blood should always be collected in leak proof, screw capped, plastic containers.

### Interpretation of Diagnostic Tests

The utility of any diagnostic test, that is their ability to detect an individual having a disease or exclude another without disease, can be determined by calculating the sensitivity, specificity, positive predictive value (PPV) or negative predictive value (NPV). Commonly, sensitivity and specificity are determined. Though these are important parameters to determine diagnostic accuracy, their values are limited to estimate probability, for which PPV and NPV may be used.<sup>4,5</sup> However, both these parameters vary with prevalence of the disease in the population and the values determined for one population cannot be applied to another population. The definition and calculation for the individual parameters are shown below:

2×2 Table for calculating parameters for diagnostic accuracy:

		True disease status		Total
		Present	Absent	
Test result	Positive	a	b	a+b
	Negative	c	d	c+d
	Total	a+c	b+d	a+b+c+d

### 1. Clinical Sensitivity

**Epidemiological definition:** Proportion of individuals with the disease which test positive (i.e., proportion of true positives) =  $a/a+c$ .

**Laboratory definition:** The ability of an analytical method to detect very small amounts of the analyte (such as an antibody or antigen).

A test which is highly “sensitive” from a laboratory perspective is also likely to be “sensitive” from an epidemiological perspective.

$$\text{Clinical sensitivity} = \frac{a = \text{True Positive (TP)}}{a+c = \text{TP} + \text{False negative (FN)}} \times 100$$

### 2. Clinical Specificity

**Epidemiological definition:** Proportion of individuals without the disease which test negative (i.e., proportion of true negatives) =  $d/d+b$ .

**Laboratory definition:** The ability of the test to react only when the particular analyte is present and not react to the presence of other compounds.<sup>6</sup>

A test which is highly “specific” from a laboratory perspective is also likely to be “specific” from an epidemiological perspective.

$$\text{Clinical specificity} = \frac{d = \text{True Negative (TN)}}{d+b = \text{TN} + \text{False positive (FP)}} \times 100$$

**3. Positive Predictive Value, or Precision Rate, or Post-Test Probability of Disease<sup>4,5</sup>:** It is the proportion of patients with positive test results who are correctly diagnosed. It is the most important measure of a diagnostic method as it reflects the probability that a positive test in an individual reflects that he/she has the disease being tested for. The PPV does however depend on the prevalence of the disease, which may vary and therefore the results should be carefully evaluated to ensure that the disease prevalence is same as that found in the patient population to which the results will be applied.

$$\text{PPV} = a/a+b = \text{True positive/True positive} + \text{False positive}$$

**4. Negative Predictive Value:** It is the probability that if the test result is negative, the individual does not have the disease of interest. As mentioned under PPV, NPV also is sensitive to the prevalence of the disease in the population.<sup>4,5</sup>

$$\text{NPV} = d/c+d = \text{True negative/True negative} + \text{False negative}$$

**5. False Positivity Rate (FPR) =  $b/b+d$ :** It is the probability that an individual will have positive test result, though he/she does not have the disease of interest. It is complimentary to clinical specificity.

**6. False Negativity Rate (FNR) =  $c/a+c$ :** It is the probability that an individual will have negative test result though he has the disease of interest. It is complimentary to clinical sensitivity.

## Quality Assurance (QA)

Microbiological investigations are necessary in the diagnosis, treatment, and surveillance of STIs and policies regarding the selection and use of antimicrobial drugs. It is, therefore, important that test reports are relevant, reliable, timely and interpreted correctly. QA has been defined by WHO<sup>7</sup> as the total process whereby the quality of laboratory reports can be guaranteed. It has been summarized as the right result, at the right time, on the right specimen, from the right patient, with the result and interpretation based on correct reference data, and at the right price.

QA is the total process whereby the quality of laboratory reports can be guaranteed.

It must be borne in mind that the quality of microbiological reports is fundamentally dependent upon the (i) quality of the specimen submitted, (ii) nature and timing of specimen, (iii) the suitability of sampling method and transport, (iv) use of transport media, and (v) transit time, and (vi) adequacy of information given to the laboratory.<sup>8</sup>

## Quality Control (QC)

The term QC covers that part of QA, which concerns the control of errors in the performance of tests and verification of test results. QC must cover all aspects of each procedure within the department. It must be practical, achievable, and affordable. All materials, stains, media, reagents and kits, equipments, and procedures must be adequately controlled. Supervisory and technical personnel should be well-qualified. Each laboratory must have standard operating procedures (SOPs) in which QA of preanalytical (while collecting specimens), analytical, and post-analytical (reporting and interpreting test results) stages of microbiological procedures should be incorporated. Laboratory personnel need to be aware of the errors that can occur during these procedures.

The laboratory should regularly have internal quality assessment (IQA) and participate in external quality assurance schemes (EQAS).

**IQA:** Each laboratory reporting results of tests should have an IQA system. This can be carried out by regular use of certified reference material as internal as well as external controls, replicate testing, retesting of retained items, and correlation of results of different characteristics of an item.<sup>8</sup>

**EQAS:** It should include testing for important pathogens using reference materials as controls. It should not be too complicated,

costly, or time consuming. Although steps may be taken in a laboratory to ensure the reliability of test results, a system of assessing a laboratory to do this to a satisfactory standard is recommended, i.e., an EQAS. Participation in EQAS should always be regarded as additional to internal QC which can assess only past performance when test results have already been reported and acted on.

The main objectives of an EQAS are to confirm that a laboratory's SOPs and internal QC procedures are working satisfactorily to help to identify errors, to improve the quality of work, stimulate staff motivation, to assure patients that the laboratory is performing to the standard required and to provide reliable results.

When comprehensive control measures and relevant assessments are in place, a laboratory can claim a level of quality assurance. QA can be seen as the sum of QC, IQA, and EQA, i.e.,  $QA = QC + IQA + EQA$ .

The diseases for which laboratory methods are useful tools have been described under:

- I. Presenting with genital ulcer
- II. Presenting with genital discharge
- III. Others

## Genital Ulcer Disease

### SYPHILIS

Syphilis, an infectious STD, is distributed worldwide. In developing countries, it is one of the leading causes of genital ulcer disease (GUD). It is caused by a spirochaete, *Treponema pallidum* (*T. pallidum*), subspecies *pallidum*. The other pathogenic species in the genera that do not produce STIs are *Treponema pertenue* causing Yaws, *Treponema carateum* causing Pinta, and *Treponema endemicum* causing endemic syphilis. The above four species cannot be differentiated morphologically or by antigenic characteristics, but only by their clinical and epidemiological features.<sup>9</sup> The infection is acquired by direct sexual contact with lesions of primary and secondary syphilis and by unsafe blood transfusion. Transplacental transmission to the fetus *in utero* is common in developing countries. The disease is systemic and the natural course of the infection may span several decades. Although syphilis is treatable, it increases HIV transmission by 3–5 fold.<sup>10</sup>

### Laboratory Diagnosis

The laboratory plays an important role in screening and confirmation of clinical syphilis. The choice of the laboratory tests varies according to different stages of the infection. HIV seropositive patients acquiring syphilis may fail to produce antitreponemal (anti-TP) antibodies or may show delayed seropositivity. Therefore, negative syphilis serology in HIV seropositive patients does not necessarily exclude a syphilitic infection.<sup>11</sup>

### Laboratory Methods

Direct demonstration of *T. pallidum* or its products like Antigen/DNA in the lesions.

### Demonstration of *T. pallidum*

**Dark Field (DF) Microscopy** A potentially sensitive and specific method for confirming the diagnosis of primary syphilis is direct demonstration of treponemes with characteristic morphology and motility, in the fluid obtained from the surface of the chancre by DF microscopy.<sup>12</sup> The test is very useful in primary and secondary syphilis and also in cases of congenital syphilis. The treponemes should be viable to distinguish *T. pallidum* from morphologically similar saprophytic spirochaetes present in the genital area.

Preparations must be examined immediately after the specimen is obtained. The result depends on the proper collection of specimen, expertise of the microscopist, and the exclusion of previous therapy with antibiotics, local or systemic. Two DF smears should be collected, as a single DF examination has sensitivity of not more than 50%.<sup>12</sup> If topical antibiotics have been used for treatment, or the ulcer has dried, material obtained by lymph node aspiration should be examined or other antigen detection methods used.

**Collection of specimen:** The lesions are cleaned carefully with gauze and saline followed by abrasion with dry gauze and gentle squeezing to get a serous exudate. Cleaning with soap or disinfectants should be avoided, only a minimum amount of tap water or saline may be used. In case of bleeding, the blood is wiped away and serous fluid collected directly on a coverslip or on a clean slide by pressing the slide directly on to the lesion. The coverslip is positioned on to the slide. Two slides are collected for better sensitivity. In case the fluid is scanty, it may be mixed with a drop of saline to give a homogenous suspension. The slide is examined immediately under a DF microscope in the laboratory adjacent to the clinic and cannot be transported to a distant laboratory, as examination of motility is important in interpretation. Biosafety precautions should be taken in handling and in discarding the waste material.

### Principle of DF microscopy and method of examination:

In DF microscopy, only light rays striking the treponemes at an oblique angle enter the microscope objective through the DF condenser, producing a luminous appearance against a dark background. Usually, the examination is done in a dark room. A few drops of immersion oil are put on the condenser, which is slightly lowered and centered. After placing the slide on the stage, the condenser is raised so that the oil touches the bottom of the slide, the end point being the illumination of the slide. After focusing under low power (10×), the material is examined under high power (40×) and then under the oil immersion lens.

**Microscopic appearance:** *T. pallidum* appears as white, very delicate organism, 0.1–0.18 µm in width and 6–20 µm in length, on a dark background.<sup>9</sup> It has 8–14 regular, tightly wound spirals with pointed and tapering ends. Motility is quick and abrupt, showing corkscrew rotation, bending, forward and backward movement, twisting, buckling, expanding, and shortening.

*T. pallidum* should be differentiated from atypical spirochaetes which are surface organisms and are not found in the depth of



lesions. These are thick, coarse, and loosely coiled. Their movement is writhing with a marked flexion and frequent relaxation of coils. Because of the presence of commensal organisms, DF examination is not recommended for oral, rectal, and non-penile genital lesions.<sup>9</sup> It is also not recommended for evaluating dry sores.

The presence of treponemes with characteristic morphology and motility confirms the diagnosis of early syphilis, even with negative serology. However, failure to find the organisms does not exclude the diagnosis of syphilis, as a DF examination may be negative due to various factors.<sup>12</sup>

**Identification of *T. pallidum* in Lesion Biopsy** In the presence of clinical symptoms suggestive of syphilis, even with negative serology, a tissue biopsy examined by immunofluorescence<sup>13</sup> or the silver impregnation stain of smears may demonstrate the treponemes.

### Detection of Antigen

**Direct Fluorescent Antibody Test (DFA–*T. pallidum*)** This test eliminates the hazards of examining infectious specimens as living, motile treponemes are not required. The test is 100% specific, differentiating *T. pallidum* from non-pathogenic treponemes. It is usually performed on lesion exudates, including rectal and oral lesions, tissues and also body fluids. After collecting specimens from lesions as in DF microscopy, the dried slide is fixed with acetone and stained with the fluorescein-labeled anti-*T. pallidum* monoclonal antibody. The visualization of apple green colored spirochaetes under fluorescent microscope (FM) gives a specific diagnosis.<sup>13</sup>

**Enzyme Immunoassay (EIA)** This test, developed commercially, detects *T. pallidum* in early lesions without the help of a microscope (Visuwell Syphilis antigen EIAADI Diagnostics).<sup>14</sup> The material collected on a swab is used to extract the antigen, which is captured by a *T. pallidum*-specific monoclonal antibody. The sensitivity of the test is comparable to DF examination but it lacks specificity.<sup>15</sup>

### DNA Investigation

DF microscopy is still considered the standard test of choice to demonstrate *T. pallidum* in exudates of mucocutaneous lesions of early syphilis and serology is also a valid tool for the clinician for diagnosis and management. However, in certain cases, evidence of the presence of DNA segments of *T. pallidum* can be used for the confirmation of the diagnosis, especially when associated with HIV infection.

**Polymerase Chain Reaction (PCR)** A sensitive, specific, and robust PCR method<sup>16</sup> reacts with various pathogenic *T. pallidum* subspecies but not with the non-pathogenic species or other spirochaetes. It compares well with a multiplex-PCR (M-PCR) test for *T. pallidum*, *Haemophilus ducreyi* (*H. ducreyi*), and herpes simplex virus (HSV).<sup>17</sup> The test is useful even in the presence of HIV infection. Clinical diagnosis and reactive syphilis serology

are less sensitive and specific than M-PCR.<sup>18</sup> It is valuable in diagnosing congenital syphilis, neurosyphilis (the serologic test available presently is only 50% sensitive), early primary syphilis and also in distinguishing new infections from old infections.<sup>19</sup> Despite its high cost, it is very useful to confirm a suspected chancre, if DF microscopy cannot be performed and serology is still negative or difficult to interpret (as in reinfection). The test can also confirm the histopathologic diagnosis of early syphilis, if a small portion of frozen tissue is available. In primary syphilis, PCR is positive exclusively in ulcerative swabs but not in blood specimens, while in secondary syphilis, 50% of the blood specimens are positive by PCR.<sup>20</sup> DFA and PCR perform equally well for detection of *T. pallidum* on touch preparations of genital lesions.<sup>21</sup>

### Serological Tests to Demonstrate Antibodies

Serology remains the mainstay of laboratory testing for syphilis, except during the very early stage of infection. Serological screening for syphilis is mandatory because there is a latent stage of infection, serious adverse effects occur if cases are not diagnosed, and relatively cheap tests and effective therapy are usually available for control.

**Natural Course of Infection and Serological Response** The natural history of syphilis is highly variable in treated and untreated cases. In untreated individuals, the course of the infection is spread over many decades and the clinical presentations are classified into early and late stages. During the course of the disease, antibodies are produced against a variety of antigens, both treponemal (TP) and nontreponemal (non-TP). Specific anti-TP IgM appears towards the end of the second week of infection; anti-TP IgG can be demonstrated later, at about 4 weeks<sup>22</sup> and symptoms also develop around that time. The immune response can be affected by treatment and by HIV infection. Following treatment of early syphilis, the titers of non-specific antibody and specific IgM decline rapidly, but specific IgG antibodies generally persist. HIV infection may reduce or delay the antibody response in primary syphilis, but in most cases the response is exaggerated.<sup>10</sup>

An important principle of syphilis serology is the detection of TP antibody by a screening test, followed by a confirmatory test. The latter should ideally have equivalent sensitivity and greater specificity than the former and be independent methodologically to reduce the chance of coincident false positive (FP) reactions. A second specimen should be tested to confirm the results obtained from the first specimen and to ensure that the patient details on the specimen are correct. A quantitative non-TP test and/or detection of specific TP IgM may be useful to assess the stage of infection and to monitor the effect of treatment. Serology cannot distinguish between the different treponematoses (syphilis, yaws, pinta, and bejel).<sup>22</sup>

The tests may be divided into two categories, depending upon the type of antigen used:

1. **Tests to detect non-TP antibodies/reaginic antibodies/non-specific tests:** These tests essentially employ a non-TP

antigen having cardiolipin, lecithin, and cholesterol,<sup>14,23</sup> and are rapid and simple to perform. Cardiolipin is a complex diphospholipid, widespread in nature,<sup>14</sup> and can be isolated from many mammalian tissues as well as from *T. pallidum*. Due to the host response to lipoidal material released from the damaged host cells and the cell surface of treponemes, anti-lipid IgG and IgM antibodies are formed which are detected by a flocculation test. The test becomes positive 10–14 days after the appearance of chancre and antibody titer gradually increases with time.

During primary syphilis, the reaginic antibodies are present, often at a relatively low level, 1:1–1:4, in about 40% of the patients; whereas in secondary syphilis, only 11% had these low titers.<sup>24</sup> The titer diminishes after treatment and the test tends to become negative over 6–8 months.<sup>23</sup> It is also negative during late syphilis. The occurrence of the “prozone phenomenon” in secondary syphilis,<sup>25</sup> results from an excess of antibody preventing antigen–antibody binding. This limits its sensitivity and therefore screening with a non-TP test alone is not recommended. The importance of repeat testing is well founded because some patients with primary syphilis will be seronegative at initial presentation.<sup>26</sup> Reactive screening tests should be confirmed with a TP test, different from that used in screening.<sup>22</sup>

There are a variety of non-TP tests, like Venereal Disease Research Laboratory (VDRL) and Rapid Plasma Reagin (RPR) test and its modification, Toluidine Red Unheated Serum Test (TRUST).<sup>27</sup> All the tests are performed using serum but can also be carried out on cerebrospinal fluid (CSF). RPR can be tested with plasma.

(i) **VDRL test:** It is a micro-flocculation test for syphilis using an antigen containing cardiolipin, lecithin, and cholesterol and has to be prepared daily. The test is usually performed as a slide test in which the serum of the patient, inactivated at 56°C for 30 minutes, is mixed with freshly prepared cardiolipin antigen, the mixture rotated mechanically for 4 minutes at 160 rpm and flocculation is detected microscopically using the low power objective. Quantitative tests using the serial dilution of the serum are also done. The test is cost-effective, rapid, simple to perform, and valuable. It can also be used as a prognostic test, as the titer declines with treatment. VDRL was reactive in approximately 75% of patients with primary syphilis, in 100% with secondary syphilis, and in 96% with latent syphilis, and was 98% specific.<sup>23,24</sup> The antigen is now synthesized,<sup>28</sup> which offers advantages in its standardization and stability.

(ii) **RPR test:** It is a field level screening test and has several advantages over the VDRL such as:

- use of stabilized antigen (6 months at 4–10°C), which need not be prepared daily.
- use of disposable printed cards instead of glass slides.

- addition of finely divided charcoal particles to the cardiolipin antigen, helping in naked eye examination of results.
- inactivation of serum is not required and the test may also be carried out with plasma.
- possibility of automation for use in centres where large numbers of sera are tested.

A modification of the test, RPR Teardrop test enables finger prick blood samples to be tested, and is ideal for field conditions.

(iii) **TRUST:** In this modification of RPR, toluidine red is used as a toner, thus obviating the need of a microscope. The sensitivity and specificity of VDRL and RPR tests and TRUST are similar.<sup>27</sup>

### **Biological false positive (BFP) reaction with non-TP tests:**

Since antibodies against a non-specific antigen shared by treponemes and normal tissues are detected in these tests, positive results are occasionally found in the sera of healthy individuals (1–2%) or patients without any clinical evidence of syphilis. These BFP reactions are labeled as acute if they disappear within 6 months and chronic if they persist longer. Acute BFP reactions are usually found in acute febrile infectious diseases, while chronic BFP reactions show a high incidence in autoimmune and related disorders and in drug addicts. VDRL test was reported to have 26% BFP reaction, significantly higher in women than in men and a 10-fold higher rate in HIV-seropositive patients.<sup>29</sup> BFP reaction is often encountered in pregnant women, leading to over-treatment. BFP-RPR reaction was found in 15% and 1.2% of HIV infected and non-infected patients, respectively.<sup>30</sup> Reactive VDRL/RPR results therefore need to be confirmed with *T. pallidum*-specific tests, which are technically demanding and not widely available in most developing countries. There is a need for simple, rapid, point-of-care (POC) type *T. pallidum*-specific test.<sup>1</sup>

2. **Tests to detect TP-IgG antibodies (Specific tests):** These tests use *T. pallidum* antigen to detect specific antibodies against *T. pallidum* cellular components. Currently, three different tests are employed as follows:

(i) ***Treponema pallidum* hemagglutination assay (TPHA/MHA-TP):** It is the easiest to perform and was the first of the specific tests used for routine screening. Red blood cells (RBCs) are treated to adsorb sonicated treponemes on their surface. When mixed with sera containing anti-TP antibodies, the cells are clumped. The sensitivity is 82% (69–90%) in primary syphilis. A negative TPHA result in the primary stage does not exclude syphilis. Positivity remains for life in most of the patients. It is a convenient test and a large number of sera samples can be tested at one time. Occasional false positive (FP) results have been reported, which could represent the effect of previous infection with endemic treponematoses.<sup>14</sup>

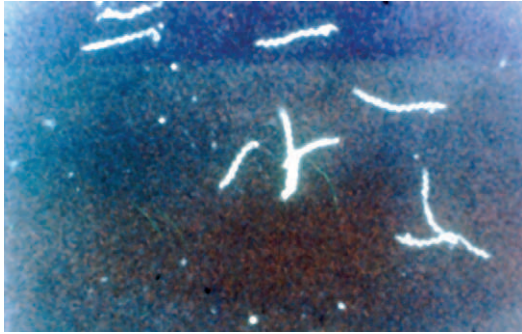


Fig. 26.1: FTA-Abs test.

(ii) **Fluorescent treponemal antibody absorption (FTA-Abs) test:** This is the most widely used test employing indirect immunofluorescence (IIF) using killed TP antigen (Nichol's strain) on a slide + patient's serum + labeled anti-human gamma globulin. The cross-reacting antibodies are removed from the patient's serum by absorption with a non-pathogenic TP antigen. The slides are examined under a fluorescing microscope (FM) for the presence of fluorescent treponemes (Fig. 26.1). It has previously been considered the most sensitive and specific of all the TP tests at all stages of syphilis. It is technically difficult to perform, and requires good quality reagents, an expensive FM and experienced microscopists. It cannot screen a large number of slides at one time. Its sensitivity and specificity are lower than that of certain other TP tests,<sup>26,31</sup> occasionally giving equivocal and false-negative results.<sup>32</sup> It is not recommended now as the first line confirmatory test.

(iii) **EIA:** This test has comparable sensitivity and specificity to the above two tests and is an appropriate alternative to the combined screening of VDRL/RPR and TPHA.<sup>20,25</sup> There are several different EIAs<sup>33,34</sup> based on different principles and different antigens (sonicates or recombinant proteins). The Captia Syphilis-G-EIA<sup>33</sup> is a single readily automated screening test in which the antigen coated on micro wells is detected by a tracer complex containing monoclonal antibody. The sensitivity and specificity are less than the FTA-Abs assay. The sensitivity is higher than TPHA in primary syphilis.<sup>34</sup> Certain newer EIAs,<sup>35–38</sup> based on recombinant antigens, are highly specific and sensitive for screening of syphilis at all stages and are significantly more sensitive than the FTA-abs. A novel immuno-capture EIA (ICE Syphilis; Murex Diagnostics, Dartford, UK), using three recombinant *T. pallidum* antigens detects more syphilitic infections in patients co-infected with HIV than does the Captia Syphilis-G EIA.<sup>38</sup>

### 3. New tests:

- (i) **Particle agglutination test (TPPA):** A Serodia TPPA test<sup>39</sup> using gelatin particles rather than RBCs as a carrier, agrees well with MHA-TP and some EIAs mentioned above, and can be used in conjunction with the RPR test.<sup>40</sup> TPPA also agrees well with a new syphilis fast latex agglutination test taking only 8 minutes to perform.<sup>41</sup>
- (ii) **Particle gel immunoassay (ID-PaGIA syphilis antibody test, Diamed):** The sensitivity of this recombinant TP antigen-based test is comparable to that of other TP tests and the specificity is even better. It is fast (reaction time of only 20 min), simple and needs minimal technical equipment.<sup>42</sup>
- (iii) **Whole-blood hemagglutination inhibition test for VDRL antibodies:** Antibody to human RBCs conjugated to VDRL liposome reacts with a diluted sample of patient's whole blood. The test has very high sensitivity and specificity, and has potential for POC testing in developing countries.<sup>43</sup>
- (iv) **Western blot (WB):** IgG WB uses a lysate of whole *T. pallidum*.<sup>44</sup> Keeping clinical diagnoses as the reference method, it has higher sensitivity and specificity than both FTA-Abs and TPHA. The agreement between WB and TP-PA is significantly better (61.5%) than that between WB and FTA-Abs (38.5%). It is a useful additional confirmatory test.
- (v) **Line immuno assay (LIA):** The sensitivity and specificity of this test is very high when compared with TPHA and IgG-FTA-Abs,<sup>45</sup> and may be used as a confirmatory test.
- (vi) **Chemiluminescence immunoassay (CLIA):** LIAISON CLIA TP Screen (DiaSorin, Saluggia, Italy), a new automated assay, demonstrates excellent sensitivity and specificity when evaluated both as a confirmatory as well as a screening test.<sup>46</sup> The Architect CLIA, another new highly automated test, is significantly more sensitive than the Murex ICE screening EIA in detecting primary syphilis, but it is significantly less specific.<sup>47</sup>
- (vii) **Immunochromatographic assay (ICA):** With TPHA results as the reference, sensitivity and specificity of the Abbott Determine Rapid Syphilis ICA are very high with minimum inter-reader variation.<sup>48</sup> However, compared to two EIAs, the sensitivity and specificity of another rapid, one step ICA, are too low to implement the test in a hospital laboratory in a developed country, but it might be useful in developing countries.<sup>49</sup>
- (viii) **Automated immunoassays:** Two automated immunoassays, Enzygnost Syphilis and ARCHITECT Syphilis TP, offer a good choice as screening tests, compared to TPHA and homemade WB. However, the use of confirmatory tests is necessary to avoid FP results.<sup>50</sup>



4. **IgM antibody tests:** In syphilis, TP-IgM antibodies appear early and can be present during late and latent syphilis. Positive IgM reactions are considered to be consistent with recent/active TP infection. The antibody level decreases after spontaneous cure and usually disappears within 6–12 months after therapy, depending on the stage of the disease. *T. pallidum*-specific IgM antibodies do not cross the placenta, and their presence in the blood of the newborn indicates congenital syphilis. Its presence in cerebrospinal fluid (CSF) with an intact blood-brain barrier indicates neurosyphilis.

Different techniques have been utilized for the detection of serum IgM antibody in syphilis and are especially useful in the diagnosis of early primary, neuro and congenital syphilis. The Captia Syphilis-M EIA has a sensitivity of 93% in primary, 85% in secondary, and 64% in early latent infection.<sup>51</sup> However, in primary stage, DF examination is a rapid and sensitive test allowing immediate diagnosis, treatment, and partner notification to prevent further transmission. EIA-IgG takes longer to become positive and is less sensitive.<sup>52</sup> The IgM capture EIA, detecting anti-TP IgM by m chain capture,<sup>53</sup> is easy to perform and is highly sensitive in detecting early infection compared to 19S IgM FTA-Abs. The Mercia IgM EIA<sup>54</sup> is as sensitive as VDRL test in monitoring treatment of primary syphilis, but not in patients treated for secondary syphilis or early latent infection. *T. pallidum* IgM immunoblot (IB) is another sensitive method to detect congenital syphilis.<sup>55</sup> A combination of routine EIA and WB-IgG and IgM may be a valid strategy for confirmatory diagnosis.<sup>56</sup>

5. **Neurosyphilis:** *T. pallidum* invades the central nervous system (CNS) in 25% of patients with syphilis<sup>57</sup> and infection is cleared from there in majority of these cases. But the remaining patients remain at risk for developing sequelae of neurosyphilis of varying degrees of severity and therefore it is necessary to perform tests with CSF. Risk factors for development of neurosyphilis in presence of HIV infection are either CD4 count of  $\leq 350$  cells/mm<sup>3</sup> or serum RPR titer  $\geq 1:32$ .<sup>58</sup>
6. **Tests on CSF:** Usually, a negative TPHA result on sera samples in patients without any clinical suspicion of neurosyphilis rules out the diagnosis. However, positive TPHA results, along with some clinical signs and symptoms, warrant a detailed examination of CSF to exclude the early invasion of the CNS. In addition to a cell count ( $> 5$  cells/ $\mu$ L), VDRL, TPHA, and FTA-Abs tests are indicated for CSF. The sensitivities of VDRL and RPR tests are only 70.8% and 75%, respectively but the specificities are very high for current neurosyphilis cases.<sup>59</sup> Therefore, only the detection of treponema-specific IgM antibodies can provide a confirmatory diagnosis of neurosyphilis. The INNO-LIA Syphilis Score<sup>60</sup> detects specific anti-treponemal antibodies in the CSF of patients with tertiary stage of syphilis.

**Table 26.2:** Possible Pattern of Laboratory Test Results in Acquired Syphilis

Interpretation	DF	VDRL/ RPR	TPHA	FTA- Abs	EIA	IgM test
Primary	+	+/-	-	+	+/-	+
Secondary	+	+	+	+	+	-
Untreated early latent	-	+	+	+	+	-
Late or late latent	-	-	+	+	+	-
Treated/partially treated	-	+/-	+	+	+	-
False +ve	-	+	-	+/-	-	-

**Interpretation of serological tests:** Reports vary on sensitivity and specificity of the available serological tests. Their results in different stages and their interpretations are given in the Table 26.2. For routine screening for syphilis, a non-TP test with confirmation by a TP test is recommended.

A non-reactive serology in the presence of clinical symptoms with a negative DF test indicates that the patient should be followed up. If treatment is started early on the results of positive DF test, the patient may remain antibody negative. However, non-reactive results for non-TP or TP tests, in the absence of clinical symptoms and HIV seropositivity, have a high negative predictive value for excluding current or previous syphilitic infection.

A reactive non-TP test indicates present infection, treated or untreated recent infection, or BFP result, which are always in  $< 1:4$  dilutions. Therefore, a titer of 1:8 or above is always diagnostic. All the low-titer positive sera in non-TP test should be confirmed by a TP test. A positive TP can indicate past infection, since patients infected with *T. pallidum* can remain positive for TP antibodies for years. Low titers in non-TP tests do not exclude syphilis and may be found in very early cases, latent or late syphilis.<sup>24</sup> Titers less than 1:4 with typical clinical signs and symptoms are considered as diagnostic of early syphilis and should be treated accordingly. The quantitative testing of VDRL should always be done. This is important in the follow-up of patients after treatment and also to obviate the problem of prozone phenomenon. However, careful interpretation of the clinical and laboratory results in each case is recommended to avoid serious social and medical implications. Whenever necessary, the test should be repeated with a fresh sample.

## CHANCROID

Chancroid is an acute highly contagious STD, associated with multiple painful genital ulcers, bubo formation, and suppurative inguinal lymphadenitis. It is common in tropical countries and is caused by *H. ducreyi*, a gram-negative, non-motile, coccobacillus ( $1.2 \mu\text{m} \times 0.5 \mu\text{m}$ ) with rounded ends. Mixed infections are common, and HIV seropositive and other immune-compromised individuals may have atypical presentations.<sup>61</sup> Therefore, the clinical diagnosis of chancroid is not very reliable (accuracy of 33–80%).<sup>62</sup> Laboratory confirmation is required for better diagnosis, especially in chancroid endemic regions of the world.



## Laboratory Diagnosis

This is based on the identification of *H. ducreyi* from genital ulcers or bubo material, and by the exclusion of other causes of genital ulcers producing a similar syndrome (Table 26.1). The direct smear examination is insensitive.

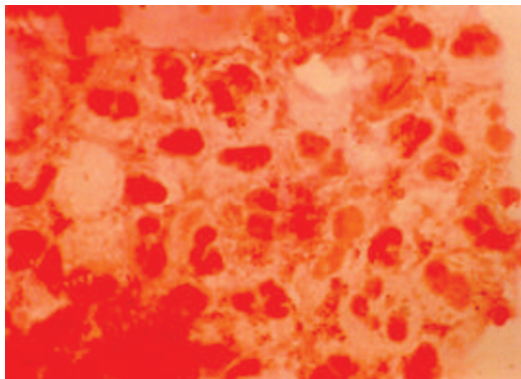
**Collection and transport of specimen:** Specimens for bacteria/antigen detection include material from ulcer and/or bubo aspirates. The ulcer is cleaned with a dry gauze or a swab to remove crusts and superficial debris by flushing with sterile physiological saline.<sup>63</sup> The specimen is collected from the base of the purulent ulcer with two sterile swabs, either cotton or calcium alginate, or by using a sterile plastic loop.<sup>64</sup> The first swab is used for smear examination, and with the second, culture media are immediately inoculated and incubated. The organism only survives for 2–4 hours on a swab at room temperature and longer at +4°C.<sup>65</sup> If clinical specimens are to be transported, a transport medium containing thioglycollate, haemin, l-glutamine, bovine albumin fraction V, and vancomycin 3 mg/L may be used.<sup>63</sup> *H. ducreyi* may remain viable in this medium for at least 24 hours at room temperature or as long as 7 days at +4°C. Amies transport medium may also be used.<sup>63,65</sup> Organisms are usually not seen in bubo pus and the culture from these sites is usually sterile. *H. ducreyi* is known to be fastidious for growth.

## Laboratory Methods

Direct non-culture detection techniques.

### Direct Microscopy

The direct examination of Gram-stained smear has been used with different degrees of success. To maintain the morphology of the bacteria, a rolled smear has been recommended. The first ulcer swab is rolled 180° on a clean glass slide and stained with Gram stain. The typical features of gram-negative slender coccobacilli, either intracellular within the pus cells or more often extracellular, singly, in long parallel chains, along the mucus threads (referred to as 'railroad tracks'), in short chains ('school of fish') or in small clusters are observed (Fig. 26.2).<sup>66,67</sup> The sensitivity of the test is around 50% or less.<sup>61,65</sup> False positive results are expected



**Fig. 26.2:** Gram-stained smear of genital ulcer showing intra- and extracellular *H. ducreyi*.

because of poly-microbial flora, often observed in genital ulcers.<sup>61</sup> The Gram stain of bubo pus is not very sensitive.<sup>68</sup>

### Detection of Antigen

**Direct Immunofluorescent (DIF) Technique** Testing of ulcer material using an *H. ducreyi*-specific monoclonal antibody appears to be useful.<sup>63,68,69</sup>

**Limulus Amoebocyte Assay** An antigen detection assay to detect *H. ducreyi* lipooligosaccharide (LOS) using a LOS-specific monoclonal antibody and an adaptation of the limulus amoebocyte assay has been described,<sup>70</sup> which has better sensitivity and specificity.<sup>63</sup> However, the reagents are not commercially available.

### DNA Investigation

**DNA Probe** The test has shown 100% sensitivity and specificity<sup>71</sup> but its usefulness in clinical practice has still to be fully evaluated.

**PCR** Compared to culture, the sensitivity of PCR is more than 95%.<sup>72,73</sup> A M-PCR technology for the detection of genital ulcer pathogens like *H. ducreyi*, HSV, and *T. pallidum* has been found to be very useful.<sup>17</sup> Two rapid multiplex real-time PCR (M-RT-PCR) reactions for *H. ducreyi*/*T. pallidum* and HSV-1/HSV-2 in ulcer swabs from persons with symptomatic genital ulcers<sup>74</sup> have shown good sensitivity and are reproducible.

### Isolation of *H. ducreyi*

Culture is the gold standard in the laboratory diagnosis of chancroid and provides an isolate for antimicrobial sensitivity testing, which provides useful information in the event of treatment failure. However, the advent of more sensitive DNA amplification techniques has demonstrated that the sensitivity of *H. ducreyi* culture is only about 75%<sup>75</sup> and many laboratories do not have facilities and adequate experience in isolating the organism. For isolation, ulcer material is optimal, followed by recently ruptured bubo exudate, while exudate from an intact bubo is least sensitive.<sup>63</sup> Ideally, the specimen should be inoculated at the bedside onto two media.<sup>76</sup>

**Culture Media and Inoculation** Various media have been compared for their suitability for the isolation of *H. ducreyi*.<sup>76–78</sup> For primary isolation, the highest sensitivity is shown by a gonococcal agar (GCA) base containing 1–2% hemoglobin, 5% foetal bovine serum, and 3 mg/L of vancomycin. Enriched Mueller Hinton chocolate agar is also a good substitute.<sup>64</sup> GCA base containing 0.2% activated charcoal, 1% bovine hemoglobin, 1% CVA enrichment, and 3 mg/L of vancomycin has also been reported to be a cheap and reliable single medium for primary isolation of *H. ducreyi*.<sup>79</sup>

The second swab collected from the ulcer base should be inoculated immediately into culture media and incubated at 32–34°C in a moist atmosphere for at least 48 hours and up to 7 days in the presence of 5–10% of CO<sub>2</sub>.<sup>80</sup> Typical colonies are

pin-point in size at 24 hours and 1–2 mm in diameter at 48–72 hours. They are yellowish or grayish yellow, raised, granular, semi-opaque, difficult to emulsify, and can be pushed across the surface of the agar with a loop.

**Identification of Colonies** The colonies are identified by a combination of the oxidase test, nitrate reduction, porphyrin test for haemin requirement and others.<sup>81</sup> *H. ducreyi* may produce beta-lactamase.

### Antimicrobial Resistance (AMR)

Clinically significant high-level plasmid-mediated AMR, spreading rapidly, has been reported in *H. ducreyi*,<sup>82,83</sup> necessitating adequate antimicrobial surveillance. AMR was reported to ampicillin, sulfonamides, chloramphenicol, tetracycline, streptomycin, and kanamycin. However, *H. ducreyi* is very sensitive to quinolones, macrolides like erythromycin or azithromycin, and the third generation cephalosporins. Most of the published studies have used the agar plate dilution technique to detect minimum inhibitory concentration (MIC), which can be done only in a reference laboratory. The E-test<sup>84</sup> is a good alternative method and owing to its simplicity and good reproducibility is well-suited for routine use in developing countries.

### Serological Tests

Dot immunobinding and EIA procedures have been reported to have utility in epidemiological studies but not for the clinical diagnosis of patients with chancroid.<sup>85</sup>

## GENITAL HERPES

Genital herpes (GH), a prominent STI, is caused by the herpes simplex viruses (HSVs), large, enveloped DNA viruses consisting of two distinct serovars HSV-1 and HSV-2.<sup>86</sup> The family contains a number of other human pathogenic viruses. The HSV-1 usually causes oropharyngeal and ocular disease and HSV-2 is usually associated with genital infections, the most common cause of GH globally. However, both the serovars have been associated with various sites and the conditions are clinically indistinguishable. HSV-2 is also known to cause recurrent infections more frequently. Primary HSV infection is often asymptomatic. The infection during pregnancy may be transmitted to the newborn.<sup>87</sup> GH presenting as a genital ulcer is usually diagnosed clinically but as there are other conditions having a similar presentation, laboratory confirmation is required for accurate diagnosis, treatment, and counseling.<sup>88</sup>

## Laboratory Diagnosis

**Collection and transport of specimens:** The specimens are obtained from vesicular fluid, cervical swab, or swab from the ulcer base. The fluid of a large vesicle is collected with a sterile syringe with 26-gauge needle or capillary tube. The small vesicles or base of open lesions are swabbed vigorously with cotton

tipped swabs on a wire shaft. If vesicles are not present, the urethral meatus of men can be swabbed. In women with HSV infection of cervix/vagina, the ectocervix and the junction of ecto and endocervix are swabbed. For asymptomatic women, one swab premoistened with saline is used to rub the clitoral hood, labia minora, labia majora, perineum, and perianal region. All the specimens are placed immediately after collection into vials containing 1 ml of viral transport medium and stored at +4°C till inoculation into tissue culture. However, for storage beyond 48 hours, freezing of the specimen at –70°C is advisable.<sup>89</sup>

## Laboratory Methods

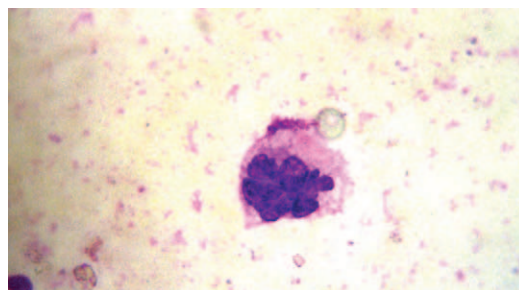
Non-culture diagnostic methods.

### Microscopy

Smears may be prepared from the base of the ulcer (Tzanck preparation) and stained by Giemsa/H&E/Papanicolaou (Pap) stain/Wright<sup>89</sup> and observed for the presence of multinucleated giant cells (Fig. 26.3) with intranuclear eosinophilic inclusion bodies surrounded by a clear halo. In the smear from ecto/endocervix stained by Pap stain, both endo and ectocervical cells may show herpes inclusion bodies. Although very rapid, inexpensive, and simple, the test is not adequately sensitive (50%) and specific (30–80%). The sensitivity depends on the quality of specimens, the staining method, and expertise of the microscopist. Cytology cannot differentiate between HSV-1 and HSV-2, or between HSV and varicella zoster virus (VZV). However, in the absence of alternative investigations, the test can be used in the diagnosis of genital ulcers.

### Detection of Antigen

**Direct Immunofluorescence (DIF)** A rapid cytospin-enhanced DIF using Chemicon HSV monoclonal antibodies is highly sensitive and more sensitive than culture. These slides contain a greater number of total cells than standard cell spots, resulting in fewer inadequate cell smears and a higher HSV detection rate.<sup>90,91</sup> The smears are stained with fluorescein-labeled monoclonal antibodies, specific to individual serovars, on two smears fixed on the same slide. Intracellular apple green fluorescence is observed in positive samples. The sensitivity is less during asymptomatic shedding. Negative results should be confirmed by a more sensitive assay.



**Fig. 26.3:** Giemsa-stained smear of a herpetic genital ulcer showing multinucleated giant cell.

**Direct Immunoperoxidase Assay (DIP)** Anti-HSV antibodies conjugated with enzyme peroxidase are added to the specimen, followed by treatment with diaminobenzidine, which reacts with peroxidase enzyme forming a reddish brown complex in the specimen where the antibody is bound to the viral antigen. Specimens from suspected HSV genital and skin lesions are tested on Hep-2 cell monolayer, examined for the presence of cytopathic effect, and also tested by DIP and DIF.<sup>91,92</sup> The test is recommended for laboratories without the facility of FM.

**EIA** A double-antibody EIA employing a polyclonal rabbit capture antiserum together with type-common and type 2-specific monoclonal antibodies as detectors is highly sensitive for identification of HSV as compared with cell culture and highly specific for typing as compared with DIF and restriction endonuclease analysis. Direct EIA (Herpcheck) alone was not sensitive enough, but in combination with culture, maximum detection is achieved.<sup>93</sup>

### DNA Investigation

**DNA Hybridization** The sensitivity and specificity of a DNA probe in comparison to standard viral isolation in tissue culture are 92% and 63%, respectively. The test is rapid and convenient, but lacks type-specific information.<sup>94</sup>

**PCR** The sensitivity of conventional PCR is much less than cell culture but specificity is very high.<sup>95</sup> Nested-PCR is an effective diagnostic and typing method for HSV with its higher sensitivity and specificity to routine viral isolation in cell culture.<sup>96</sup>

A RT-PCR is a highly reproducible, rapid (<4 hours), and labor efficient method for HSV-2 detection in genital swabs. It significantly increases HSV detection in both early (<5 days) and late (≥5 days) presentations and in both first and recurrent episodes.<sup>97</sup> An in-house RT-PCR hydrolysis probe assay for the detection of HSV from various clinical samples performs well and combined with careful clinical interpretation, the detection, differentiation, and quantification of HSV from mucocutaneous swab samples should improve.<sup>98</sup>

A M-PCR assay for detection of HSV-1 and HSV-2 DNA has higher sensitivity and improved turn around time than traditional culture of HSV in MRC-5 cells with confirmation by DIF. Subtyping may also be done by PCR.<sup>99</sup> A M-PCR-based reverse line blot (M-PCR/RLB) assay developed to detect 14 urogenital pathogens or putative pathogens, including HSV1 and HSV2, in FVU from men, is accurate, convenient, and inexpensive.<sup>100</sup>

A pol PCR is a cheaper and more easily reproducible method for typing HSV isolates as compared to the DIF test and could replace it as availability of PCR machines is now more widespread than fluorescence microscopes in a country like India.<sup>101</sup>

### Isolation

Viral culture is considered as the gold standard in laboratory diagnosis of HSV. The common cells used are the African green monkey kidney (Vero), baby hamster kidney, guinea pig embryo, human amnion cells, human diploid fibroblasts, etc. Cytopathic

effects (CPE) are usually observed as early as 18–24 hours but may take 4–6 days, depending upon the concentration of virus in the specimen. It includes the rounding of cells, which later becomes swollen and refractile and finally die and detach from the surface of the culture vessel. Various immunological methods like neutralization, DIF, and nucleic acid hybridization procedures may be used to identify the isolates when unusual CPE occurs or when the patient is asymptomatic. DIF is commonly used with fluorescein-conjugated type specific anti-HSV antisera.<sup>92,101</sup> Shell vial culture remains the test of choice for obtaining maximum diagnostic yield from the sample.<sup>102</sup>

### Serological Tests

As mentioned earlier, with any diagnostic test, the prevalence of the disease in the population is essential for interpreting the test result. During a primary episode of GH, when there is no antibody/low level of antibody in the acute sample, serology can help in diagnosis if there is a four-fold rise in titer in the repeat sample. However, less than 10% patients with recurrent episodes of the disease show a rise in antibody titer in the convalescent sera. The absence of rising titer does not exclude HSV infection. Patients with subclinical or atypical presentations cannot be identified by most HSV antibody tests. Sensitive tests like EIA for IgM detection are available for the diagnosis of acute episodes. However, IgM-specific antibody responses are not always restricted to primary infections; reactivation or reinfection may result in IgM response.

### Type-Specific Serology (TSS)

Accurate identification of individuals with GH is necessary for optimal patient management and prevention of transmission. It is also important to know the HSV type to counsel on the natural history of infection and risk of transmission. TSS assays have overcome the technical problems associated with earlier cross-reaction in HSV serological assays.<sup>103</sup>

**POC Kit HSV-2** A HSV-2 IgG-specific antibody lateral-flow immunochromatographic assay (LFIA) based on colloidal gold nanoparticles has excellent sensitivity, specificity, and concordance for both serum and whole-blood samples, compared to that of both HSV-2 EIA and IB.<sup>104</sup>

**EIA** Two commercial EIAs (Herpe-Select 2 and the Euroimmun EIA) use purified glycoprotein gG-2 specifically for detection of HSV-2-specific IgG antibodies. The concordance of positive and negative results between the two is 100%.<sup>105</sup> Commercial EIAs compare well with the results obtained by monoclonal antibody-blocking EIA (MAb-EIA). The Kalon EIA has a higher specificity than the Herpe-Select EIA.<sup>106</sup>

**Express Assay (EA)** This new POC test provides results similar to EIA for the identification of HSV-2 type-specific antibody among pregnant women and in conjunction with confirmatory EIA testing improves the PPV of HSV-2 serodiagnosis.<sup>107</sup>

PCR has, by far, the greatest sensitivity and should be the test of choice for symptomatic cases. HSV-2-TSS is indicated



for patients with genital lesions in whom antigen detection, culture or PCR fail to detect HSV and for patients who are asymptomatic but have a history suggestive of GH. HSV-2-TSS is further indicated for patients infected with HIV and along with HSV-1 TSS, the test may be considered as appropriate in (i) evaluating infection and/or immune status in couples discordant for GH, (ii) women who develop their first clinical episode of GH during pregnancy, (iii) asymptomatic pregnant women whose partners have a history of GH or HIV infection, and (iv) women contemplating pregnancy or considering sexual partnership with those with a history of GH. The above tests should be performed in conjunction with counseling of infected persons and their sex partners.<sup>108</sup> Clinicians need to be aware of the test limitations and should consider whether the results influence the treatment or outcome, otherwise testing is a waste of limited health resources and is not indicated.<sup>109</sup>

### GRANULOMA INGUINALE (DONOVANOSIS)

Granuloma inguinale is characterized by chronic granulomatous, beefy, erythematous, painless lesions with whitish border, involving skin, mucous membrane, and the lymphatic system of the genitalia and perianal area. It is caused by *Calymmatobacterium granulomatis* (*C. granulomatis*). The organism is a gram-negative bacterium (1.5  $\mu\text{m}$   $\times$  0.7  $\mu\text{m}$ ) and is usually found in large mononuclear cells within clear spaces or vacuoles. It is also called a Donovan body (DB), after the physician who first visualized the organism in such a lesion. The disease has recently been the subject of renewed interest after a long period of relative obscurity. *C. granulomatis* and human *Klebsiella* species are ultrastructurally, morphologically, and antigenically indistinguishable. Phylogenetic analysis confirms close similarities and *C. granulomatis* is proposed to be reclassified as *Klebsiella granulomatis* *comb nov.*<sup>110</sup>

### Laboratory Diagnosis

**Collection of tissue specimen:** The diagnosis is usually made from tissue smears. The border of the well-defined ulcer is cleaned with sterile gauze soaked in saline and wiped clean. A small piece of tissue is removed with a scalpel, a punch biopsy, forceps or the sharp end of a broken slide and kept on a clean grease free microscope slide.<sup>111</sup> Another grease-free slide is held on the piece of tissue and pressed firmly so that the tissue is crushed between the two slides.<sup>112</sup> The crushed tissue is spread on the slide and the smear so obtained is allowed to dry in air.

### Laboratory Methods

Non-culture diagnostic methods.

#### Microscopy

The smear is stained with the Leishman/Giemsa<sup>111</sup> and other Romanowsky stains for microscopy. Slow Giemsa, an overnight technique was found to have a 100% success rate in one study.<sup>113</sup> A 1 minute staining technique has been described.<sup>114</sup> The smear

is found to contain predominantly mononuclear phagocytes. DBs are observed as bluish purple coccobacilli of about 20–90  $\mu\text{m}$  diameter inside big clear to acidophilic vacuoles/capsules. The bacteria are pleomorphic with prominent polar granules and may typically be seen as “halters” or safety pins.

#### Histopathology

The organism can be demonstrated by histopathological examination of the tissue and it may be helpful in the differential diagnosis of other similar conditions. It shows an ulcer with an infiltration of plasma cells, neutrophils and histiocytes with complete absence of lymphocytes. Presence of DBs within the histiocytes in cells stained with Warthin Starry silver impregnation stain helps in the diagnosis.<sup>115</sup>

#### DNA Tests

**PCR** The first PCR assay designed to differentiate *C. granulomatis* from other *Klebsiella* species<sup>116</sup> has been successfully incorporated into a colorimetric detection system for *C. granulomatis* with two levels of specificity.<sup>117</sup>

#### Isolation

Cultivation of *C. granulomatis in vitro* was done in the past using media containing some of the growth factors contained in egg yolk.<sup>118</sup> Later, it was grown in a human monocyte co-culture system<sup>119</sup> requiring fresh monocytes from healthy donors. Successful culture of the organism onto cycloheximide-treated HEp-2 cell monolayer is now reported. The organisms appear as pleomorphic bacilli with characteristic bipolar staining and “safety pin” appearance.<sup>120</sup>

#### Serology

**Indirect Immunofluorescence (IIF):** The test for the detection of antibody in the serum shows high sensitivity and specificity.<sup>121</sup>

## Presenting with Genital Discharge

### GONORRHOEA

Gonorrhoea is one of the oldest known diseases in human beings, transmitted almost exclusively through sexual contact. The causative agent is *N. gonorrhoeae*, a gram-negative diplococcus (GNDC) with adjacent sides concave (coffee bean shaped). It is always considered as a pathogen of great clinical significance.<sup>122</sup> In men, the organism commonly produces anterior urethritis, presenting with dysuria and purulent discharge. Many other organisms like *C. trachomatis* produce a similar syndrome called non-gonococcal urethritis (NGU) and it is difficult to make an absolute distinction between the two on clinical grounds. In women, a wide range of clinical presentations is known, the most common being cervicitis. Asymptomatic infections are common. An important complication in women is pelvic inflammatory disease (PID). In neonates, ophthalmia neonatorum or neonatal



conjunctivitis is known. Epidemiological studies suggest that there is greater risk of acquiring HIV in the presence of gonorrhoea.<sup>123</sup>

## Laboratory Diagnosis

Microbiological tests are mandatory for the diagnosis in both sexes. Rapid diagnosis, using careful laboratory techniques, is important for the control of infection in the community, as the disease has got a short incubation period and high infectivity. This includes careful selection and collection of proper specimens and their immediate transport to the laboratory for culture and other techniques. The preliminary diagnosis is ideally done in the clinic with facilities for direct microscopy, and treatment can follow immediately in about 95% of men and 60% of the women.

### Collection of Specimen in Men

**Urethral swab:** The most important site for collection of a specimen in heterosexual males is the urethra. While wearing sterile gloves, the specimen is collected at least 2 hours after the patient has urinated, as voiding decreases the amount of exudate and reduces the chances of detecting the organisms. The prepuce is retracted, the tip of the meatus cleaned with normal saline and the pus is collected directly on the sterile swab if purulent discharge from the urethral meatus is present. If no discharge is seen, the urethra is gently stripped/milked towards the orifice to express the discharge. If no discharge is obtained, a sterile thin calcium alginate swab with a flexible wire shaft (intraurethral swab)/sterile bacteriological loop is inserted 2–3 cm into the urethra and rotated for 5–10 seconds to gently scrape the mucosa of the terminal part of the urethra. In case no evidence of urethritis is found on examination, but there is a history of contact, the patient is asked to hold urine overnight, urethra massaged and the discharge, if any, is collected and processed similarly.

**Urine:** First void urine (FVU) may also be a useful specimen.<sup>2</sup> The first 10–15 ml of the early morning urine is collected in a sterile plastic container with a large opening. Urine samples should be processed immediately, as it may be toxic for *N. gonorrhoeae* on standing.<sup>124</sup>

### Collection of Specimen in Women

**Endocervical swabs:** In women, usually an endocervical specimen is collected. In menopausal women or in those who have undergone hysterectomy, cervical specimens are not collected since gonococci in this age group involve the vagina, not the cervix. No antiseptics, analgesics or lubricants should be applied. A sterile vaginal speculum is inserted in the vagina and the ectocervix is inspected in ample light. The speculum can be moistened with warm water. Sterile non-cotton swabs are inserted for 2–3 cm into the endocervical canal, rotated from side to side for a few seconds to allow the absorption of the exudate and withdrawn.

**Urethral swabs:** All the precautions, as described for males, should be observed. If pus is present on the urethral meatus, it is collected with a sterile non-cotton swab; otherwise, the urethra is massaged against the symphysis pubis and the exudate is collected.

**Vaginal swab:** Using a speculum, the posterior fornix is swabbed for a few seconds. In prepubertal girls, the discharge is collected with a swab without introducing a speculum.

**Self-obtained vaginal swabs (SOVSs):** Self-collected specimens, such as urine and vaginal swabs, can be successfully used to diagnose STIs, when they are used with nucleic acid amplification assays. This eliminates the necessity for a clinician-performed pelvic examination in women for sample collection.<sup>125</sup>

### Collection of Specimen in Both Sexes

The sites swabbed in homosexual men/women are the rectum, urethra, and oropharynx.

**Rectal swab:** If recent anal intercourse has occurred, a proctoscope is inserted first, followed by a swab stick, 3 cm into the anal canal rotating it for 10 seconds to collect exudate/mucus or mucopus from the crypts just inside the anal ring.

**Pharyngeal swab:** If orogenital contact with an infected person is suspected, a specimen is collected from the tonsillar crypts and bed of pharynx.

Cotton, calcium alginate, Dacron, rayon or polyethylene terephthalate (PET) swabs with plastic or aluminium shaft, or a bacteriological loop may be used for collection of the specimen. Calcium alginate may sometimes be toxic to certain gonococcal strains.<sup>126</sup> Two swabs should always be collected, one for direct microscopy and the other for culture. Transport media should be used if the laboratory is not in the vicinity of the clinic.

**Transport of specimens:** The best results for the isolation of the organism are obtained by bedside culture, as *N. gonorrhoeae* is highly susceptible to environmental conditions. If the laboratory is not in the vicinity of the clinic, the specimen should be transported on nutritive media such as Transgrow<sup>127</sup> or Jembec<sup>128</sup> for maximum recovery. These systems consist of a selective medium, usually present in a small chamber containing CO<sub>2</sub> or a CO<sub>2</sub> generating system. The media can be inoculated directly from the patient and transported to the laboratory either before or after incubation, or after growth appears (Fig. 26.4). Specimens can also be inoculated on non-nutritive transport media like Stuarts or Amies. A newly modified Amies charcoal swab transport system<sup>129</sup> (StarSwab SP131X) is capable of maintaining the viability of *N. gonorrhoeae* for at least 24 hours and reinforces the need for adequate sampling and timely processing of specimens to maintain optimum performance. Dry swabs should not be sent as the gonococci are susceptible to drying. The isolation rate after the transport of specimens in a non-nutritive medium at room temperature (20–25°C) is approximately 100% within 6 hours and 90% within 12 hours.<sup>130</sup> After 24 hours, recovery may not be possible, especially in asymptomatic patients.

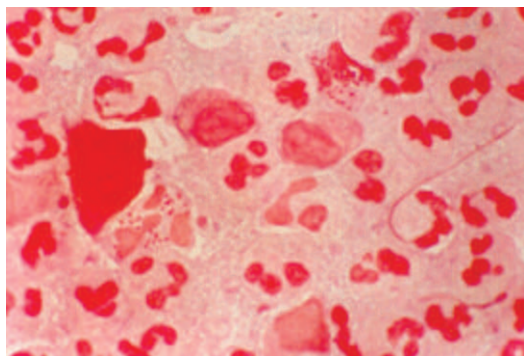


Fig. 26.4: Smear showing gram-negative diplococci.

## Laboratory Methods

Direct non-culture techniques.

### Microscopy

Microscopy of a Gram-stained smear, using purulent material expressed from the urethra, cervix, rectum or conjunctiva is an important test for the diagnosis of gonorrhoea, especially in resource poor settings. It provides an immediate diagnosis in the clinical setting. However, in homosexual men it is always better to attempt culture and further identification, as *Neisseria meningitidis* may be present in such specimens. A smear for microscopy is prepared, fixed, and stained with gram stain. Using a bright light microscope, the smear is examined with 100× objective. The Gram-stained smear of urethral discharge in a typical positive case shows a large number of characteristic kidney-shaped GNDC lying within the polymorphonuclear leukocytes (PMNL). A slide is examined for at least 2 minutes before reporting as negative. The smear is equivocal if there are only extracellular GNDC without any intracellular ones.

**Sensitivity and Specificity of Microscopy** In men with symptomatic urethritis, the sensitivity of the urethral smear is 90–95% and specificity is 95–100%. In women, sensitivity of the cervical smear is 50–70% and specificity is 95–100%.<sup>131</sup> A direct microscopic test is not recommended for pharyngeal smears. The test is not useful as a test of cure in urethral gonorrhoea. It is less reliable in the diagnosis of long-standing and asymptomatic infections.

### Direct Detection of Gonococcal Antigen

**EIA** EIA (Gonozyne)<sup>132</sup> utilizes a polyclonal antibody to detect gonococcal outer membrane protein. It has good sensitivity and specificity, compared with swab culture. Compared to swabs, urine has less sensitivity and specificity in both sexes, especially females.

### DNA Investigation

The molecular-based approaches now available are more accurate, cost-effective, and acceptable to patients. Compared with unamplified direct probe assays, nucleic acid amplification

tests (NAATs) have better detection rates for *C. trachomatis* and *N. gonorrhoeae*, and have provided clinical laboratories with advantages over traditional culture methods. These include increased sensitivity with regard to limit of detection allowing high throughput without the need for viable organisms and the ability to perform multiplex assays for the simultaneous detection of *N. gonorrhoeae* and *C. trachomatis*.<sup>133</sup> There are some limitations for its use e.g. in (i) cases of sexual abuse where 100% specificity is desirable, (ii) requests for a test-of-cure, (iii) non-genitourinary specimens, (iv) cost, (v) risk of carryover contamination, (vi) inhibition, and (vii) inability to provide antibiotic resistance data.<sup>134</sup> In addition, there are sequence-related limitations that are unique to *N. gonorrhoeae* NAATs. Overall, the *N. gonorrhoeae* species continue to present a considerable challenge for molecular diagnostics.<sup>133</sup>

- 1. DNA probe assay:** The direct probe assays are best suited for high-volume testing among high-risk groups and for settings in which NAAT is unaffordable.<sup>135</sup> Probe assay chemiluminescence enhanced test (*Gen Probe PACE* test), a non-isotopic assay for the direct detection of *N. gonorrhoeae* in urogenital specimens has been modified (*PACE-2* test *Gen-Probe*, San Diego, California). It is equivalent to the culture method in terms of sensitivity, specificity, PPV, and NPV in both symptomatic and asymptomatic women and can serve as a suitable screening and diagnostic test for gonorrhea in women.<sup>136</sup> In symptomatic men, there is excellent agreement between Gram stain and *PACE 2*.<sup>137</sup> A Combo probe 2C combining probes against *N. gonorrhoeae* and *C. trachomatis* performs very well in endocervical specimens.<sup>138</sup>
- 2. Dot blot hybridization and *in situ* hybridization with DNA probes:** On comparison with Gram staining and culture, it is a fast and sensitive method for the detection of gonococci in urethral exudate from men.<sup>139</sup>
- 3. Amplification methods:**

(i) **PCR:** The sensitivity and specificity of an in-house PCR for the detection of *N. gonorrhoeae* from urogenital samples are very high.<sup>140</sup> The Roche Cobas Amplicor M-PCR assay can simultaneously detect both *C. trachomatis* and *N. gonorrhoeae* in endocervical and urethral swabs, and urine specimens. The target sequence is known to be present in some strains of commensal *Neisseria* species, including *Neisseria cinerea* and *Neisseria subflava*, necessitating the use of a second PCR assay to confirm positive results.<sup>141</sup> Overall, there is good agreement between the confirmed PCR assay and culture. The sensitivity of this assay in urine specimens in women is too low to recommend its routine use to test for gonorrhoea.<sup>142</sup>

A sensitive and specific *RT-5-nuclease PCR assay* can be used as an accurate and rapid test.<sup>143</sup> *RT-PCR* assay is a valuable supplement to the culture technique for diagnosis of *N. gonorrhoeae*, especially for samples from extra-genital sites such as pharynx

and rectum.<sup>144</sup> In resource-limited settings, pooling of urogenital specimens to detect *C. trachomatis* and *N. gonorrhoeae* by PCR is a simple, accurate, and cost-effective procedure, compared to individual testing.<sup>145</sup>

- (ii) **Transcription-mediated assays (TMA) and Strand displacement assay (SDA):** TMA using APTIMA *C. trachomatis* (ACT) and APTIMA *N. gonorrhoeae* (AGC) identifies the respective infections in symptomatic and asymptomatic patients and is suitable for screening males using urethral swabs or urine.<sup>146</sup> However, use of SDA, for the detection of gonococcal infection in low prevalence populations is controversial because of the likelihood of FP results. There is high concordance between the above three NAATs,<sup>147</sup> which are increasingly the method of choice for the detection of *N. gonorrhoeae* and *C. trachomatis* in extra-genital sites in males having sex with males (MSM).<sup>148</sup>
- (iii) **Ligase chain reaction (LCR):** The overall performance of LCR with swabs or FVU and pharyngeal and anorectal specimens is better than that of culture for the diagnosis of genital or extra-genital gonorrhoea.<sup>149</sup> The results of Abbott LCR and Gen Probe PACE-2 compare well with culture.<sup>150</sup> Pooling of urine specimens is a cost saving technique.<sup>151</sup>
- (iv) **Nucleic acid sequence-based amplification (NASBA):** In women, using cervical and urethral specimens, the sensitivity of both microscopy and culture are very low and that of NASBA, 90.9%, compared to PCR. In men, using urethral specimens, microscopy, culture, and NASBA displayed a sensitivity of 75%, 50%, and 100%, respectively.<sup>152</sup>

### Isolation

Culture is advised in (i) the diagnosis of rectal, oral, disseminated and asymptomatic infections in both sexes, (ii) determining antimicrobial susceptibility, (iii) assessment of treatment efficacy, and (iv) medico-legal cases. The reliability of culture depends on the technique of collection, number of sites sampled, method of transportation, composition and quality of culture media, and methods of identification.

**Culture Media and Inoculation** The maximum sensitivity of culture is achieved when a non-selective culture medium like chocolate agar is used in addition to a selective medium. Selective enriched medium with a rich nutrient base supplemented with blood, either partially lysed by heat (chocolate agar) or completely lysed by saponin, is useful for the isolation. These are Modified Thayer Martin Medium (MTM),<sup>153</sup> New York City (NYC) agar,<sup>154</sup> Lysed blood agar medium or GC Lect medium.<sup>155</sup> In some geographical areas, up to 3–10% of gonococci are susceptible to 3–4 mg/L of vancomycin used in selective media; hence, supplements with reduced vancomycin (2 mg/L) or lincomycin may be used.<sup>156</sup>

The specimen swab is rolled over approximately one quarter of the surface of the plate and the inoculum is spread with a bacteriological loop over the remaining part of the plate and incubated. The inoculated plates are incubated at 35–36°C in a humid atmosphere (70% humidity) containing 3–7% CO<sub>2</sub>, which can be provided in a CO<sub>2</sub> incubator, a container with a CO<sub>2</sub> generating tablet or a candle extinction jar with a white unscented, non-toxic candle.

**Presumptive and Confirmatory Identification of Colony** The typical colonies are seen after 24–48 hours (Fig. 26.5) and can be identified presumptively by the Gram stain and oxidase test (Fig. 26.6) and differentiated from meningococci by the superoxol test and rapid carbohydrate utilization test (Fig. 26.7).<sup>157</sup> The organism is superoxol and oxidase positive and ferments glucose.

Immunological tests using monoclonal antibodies for fluorescence/co-agglutination, or tests based on enzyme systems used on primary isolation plates are highly sensitive, specific, and rapid for confirmatory identification of *N. gonorrhoeae*.<sup>158</sup> Sensitivity of the Phadebact (R) Gonococcus Test, a slide co-agglutination test, is better than the Difco FTA test for the identification of *N. gonorrhoeae* isolated from primary plates and FP results due to cross-reactions with non-pathogenic *Neisseria* are uncommon.<sup>159</sup>

**Antimicrobial Susceptibility Testing** This is not always required for providing treatment to individual patients but may be needed to monitor (i) trends in resistance and to provide basic susceptibility information to national planners, (ii) clinical efficacy of recommended treatment regime in order to provide



Fig. 26.5: Typical gonococcal colonies.

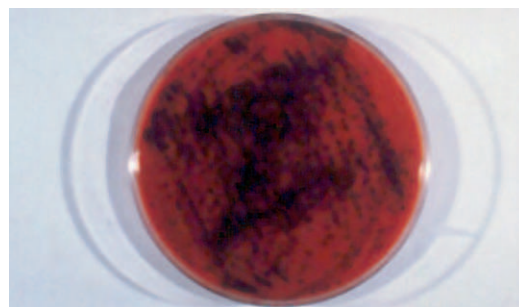


Fig. 26.6: Oxidase test on gonococcal colonies.



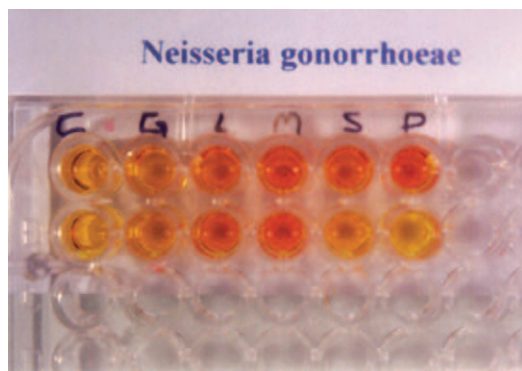


Fig. 26.7: Rapid carbohydrate utilization test.

information to clinicians in cases of treatment failure, and (iii) for the study of new antimicrobial agents.

Usually, the disc diffusion technique is preferred. Determination of minimum inhibitory concentration (MIC) is recommended only for the reference laboratory. The E-test (AB-Biodisk, Solna, Sweden) is an effective, simple alternative to the reference agar dilution method for direct quantification of *N. gonorrhoeae* susceptibility.<sup>160</sup>

### Antimicrobial Resistance (AMR) in *N. gonorrhoeae*

Resistance of *N. gonorrhoeae* to antibiotics, including quinolones, has increased rapidly in recent years and has reduced the options for treatment. Globally, gonorrhoea has spread widely due to the emergence of multidrug resistance, consequent to uncontrolled use of antibiotics. Now many developed countries recommend the use of third-generation cephalosporins instead of quinolones for the treatment of gonorrhoea. Gonococcal resistance to third-generation cephalosporins given orally is emerging in Japan and elsewhere.<sup>161</sup>

According to a report on the status and trends of AMR patterns of *N. gonorrhoeae*, isolated in sentinel laboratories in the Gonococcal Antimicrobial Susceptibility Programme (GASP) under SEAR of WHO,<sup>162</sup> penicillin, tetracycline and ciprofloxacin resistance rose significantly in Indian laboratories. Strains less sensitive to ceftriaxone, but resistant to spectinomycin were reported. In Sri Lanka, gonococci showed high resistance towards penicillin (96.8%). Bangladesh reported *N. gonorrhoeae* resistant to ciprofloxacin (76%), penicillin (33%), and tetracycline (50%), and with decreased susceptibility to ceftriaxone (1.5%). Spectinomycin resistance was not observed. The report stresses the necessity for continuous surveillance of AMR pattern in this region and establishing antimicrobial policy guidelines to manage this common and important STI pathogen.

A significant increasing trend of penicillin and ciprofloxacin resistance up to 2003 and 2004 was observed in a recent study from India. Tetracycline-resistant *N. gonorrhoeae* increased significantly. Only one isolate showed resistance to spectinomycin and nine had reduced susceptibility to ceftriaxone. A substantial

proportion (23.3%) of strains was multidrug resistant (MDR). The search for new effective agents needs to be initiated to respond to the emergence of resistant isolates.<sup>163</sup> Globally, a sustained and integrated effort to reduce rates of gonorrhoea and the misuse of antibiotics is required to prevent further emergence and spread of MDR strains.

### CHLAMYDIA TRACHOMATIS INFECTION

Recognized since 1970, *C. trachomatis* is among the most common bacteria associated with STIs. Serovars D-K cause genital chlamydia infections, e.g. NGU and post-gonococcal urethritis (PGU) in males, mucopurulent cervicitis and proctitis in females, and inclusion conjunctivitis in adults and neonates. It produces a variety of complications like PID and infertility in females and epididymitis and infertility in males. Serovars L1, L2, and L3 cause lymphogranuloma venereum (LGV).

*C. trachomatis*, a gram-negative bacterium, is an obligate intracellular parasite and can only grow in tissue culture. It produces intracytoplasmic, perinuclear, acidophilic inclusion bodies during its life-cycle. Other species of *Chlamydia*, like *C. pneumoniae* and *C. psittaci* (transmitted from birds to humans), cause respiratory illnesses. STIs due to *C. trachomatis* are very common in the industrialized world. Many people, especially women, are symptom free and infections are never diagnosed or reported. The infection is common among young people and is more common in heterosexuals.

### Laboratory Diagnosis

**Collection and transport of specimens:** The gold standard in the diagnosis of genital chlamydia infection prior to the advent of NAATs used to be tissue culture. The collection of specimens and use of the appropriate swab and transport media are vital to the success of tissue culture. Plastic or metal shafts are better than swabs with a wooden stick.<sup>164</sup> Cotton-tipped swabs, if used, should be tested for toxicity.<sup>165</sup> Cytobrush is an ideal device and is more efficient at the removal of cervical mucocolumnar junction cells for the culture of *C. trachomatis*.<sup>166</sup> Recently, modified sanitary napkin (wearing for 4 hours) was found to be an effective non-invasive device for self collection of specimens to detect urogenital *C. trachomatis* infection.<sup>167</sup> In patients with genital discharge, the anterior urethra and cervix are the most important sites. Sometimes, rectal mucosa and throat can be swabbed. For LGV, the specimens collected are bubo pus, rectal swabs, and biopsy material.

**Urethral swab:** A fine, flexible shafted swab is introduced 3–4 cm into the urethra and the mucosa is gently scraped by rotating for 5–10 seconds.

**Endocervical swab:** Forceps with gauze or a large cotton-tipped swab are used to remove secretions from the ectocervix. A specimen swab is inserted 2 cm into the cervical canal and gently rotated for 10 seconds scraping the endocervical



epithelial cells, concentrating on any inflamed area or where follicles are seen.

**Bubo pus:** The bubo pus may be aspirated with a syringe and needle, if necessary, after injecting sterile saline. The pus is homogenized before inoculating into tissue culture.

**Urine:** 10–15 ml of FVU should be collected in a sterile vial.

**SOVS:** Discussed earlier.

FVU is a suitable non-invasive sample type for diagnosis of urogenital *C. trachomatis* infection in men, as its chlamydia load does not differ significantly from that of urethral swabs. Given their higher organism load compared with FVU, SOVSs are the preferred non-invasive sample type for women.<sup>168</sup> First Burst is a urine collection device which collects the first 4–5 ml of FVU and yields a specimen with a six-fold higher *C. trachomatis* organism load than the regular urine cup, by quantitative PCR. This has improved the sensitivity of a rapid test for chlamydia.<sup>169</sup> A novel postal urine transport method is used in self collection based screening of *C. trachomatis*. Urine is desiccated using an anhydrous gel composed of superabsorbent polymer and buffering agent. The gel-based method is suitable for the detection of *C. trachomatis* by PCR. In addition, ease of use, effectiveness at ambient temperature and low cost makes it well-suited for population-based *C. trachomatis* screening, particularly for geographically and socially isolated individuals.<sup>170</sup>

Specimens for culture are collected in a sucrose phosphate (SP) transport medium in cryo-vials and should be sent to the laboratory within 2 hours, to be stored at  $-70^{\circ}\text{C}$ , before inoculating tissue culture. The *chlamydiae* are viable for 24 hours at  $2-8^{\circ}\text{C}$  and if the delay in inoculation is more than 24 hours, freezing at  $-70^{\circ}\text{C}$  is advisable.<sup>171</sup>

## Laboratory Methods

Direct non-culture techniques.

### Persistent Urethral Leukocytosis

More than 4 PMNL per oil immersion field (OIF) on Gram stain of urethral secretions, or persistent pyuria in an FVU, in males, indicates ongoing urethritis. In females,  $>30$  PMNL per OIF on gram-stained smears of cervical mucus is suggestive of chlamydia cervicitis.<sup>172</sup>

### Leukocyte Esterase (LE) Testing

A combination of above and LE testing of urine is sensitive in identifying chlamydia-infected individuals but the specificity is poor and this can be used as a screening test to select patients, especially males, for specific *C. trachomatis* testing.<sup>173</sup>

### Direct Microscopy

**Giemsa Staining** The value of the examination of a Giemsa-stained smear from genital specimen for detection of inclusion

bodies is limited and is not recommended for routine laboratory diagnosis as it is time-consuming and not sensitive. Cervical scrapings are difficult to read because of the presence of mucus, cell debris, bacteria, etc. in the background. However, it is a simple technique and the microscopist may be rewarded if careful examination is done. In a Giemsa-stained smear, the nucleus of the epithelial cells stains pink. The elementary bodies (EB) of *C. trachomatis* stain purple, but the perinuclear intracytoplasmic inclusions in epithelial cells containing the reticulate bodies (RB) are strongly basophilic (Fig. 26.8) and tend to stain blue. Cytoplasmic areas around the inclusion are grey.<sup>171</sup>

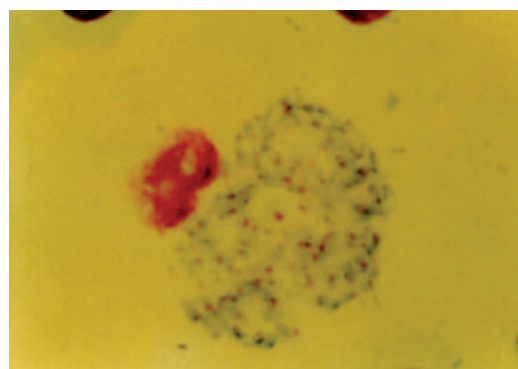
**Iodine Staining** The scrapings are air dried, fixed in absolute methanol and stained with Lugol's iodine. The glycogen containing mature inclusion bodies of *C. trachomatis* stain brown in smears. The method is not sensitive.

### Detection of Antigen

As culture is slow and labor intensive, non-cultural techniques without these drawbacks have come to dominate.

**DFA Test:** This is a rapid diagnostic test carried out on clinical specimens using monoclonal fluorescein-labeled anti-chlamydia antibodies against the species-specific epitope of major outer membrane protein (MOMP) or genus-specific lipopolysaccharide (LPS). For better detection, the specimen may be centrifuged on the slide.<sup>174</sup> Free EBs appear as bright apple green dots, 300 nm in diameter, with a smooth margin. (Fig. 26.9). Ideally, at least 10 EBs should be seen before making a positive diagnosis.<sup>175</sup> The method is sensitive in symptomatic patients, permits an assessment of the quality of the specimen and is good for small batches, but is expensive, requiring expertise and high-quality FM. The specificity is high when compared to culture.<sup>176</sup>

**EIA** Commercial EIA kits, following different principles, are available for the detection of chlamydia antigen (usually LPS) in clinical specimens. Appropriate collection kits containing special swab sticks and transport media, provided along with the kits, should be used for the test. The antigen is extracted from the specimen either by heating or by detergent. The specificity and sensitivity of



**Fig. 26.8:** Giemsa-stained smear of cervical scraping showing chlamydia inclusion body.



**Fig. 26.9:** Direct fluorescent antibody test—fluorescent stained elementary bodies of *Chlamydia trachomatis*.

DFA test and EIA are similar. EIA is the test of choice in many laboratories because of its simplicity. The advantages over the DFA technique are that a large number of specimens may be processed at one time and reading is more objective. In asymptomatic males, urine immunoassay screening in combination with confirmation by DFA has been used.<sup>175</sup> The sensitivity and specificity are lower than DNA-based tests.<sup>176</sup> Specificity may be increased either by confirmation using another assay like DFA,<sup>177</sup> or by using kits with confirmatory assays using blocking antibodies.<sup>178</sup>

**Rapid Assays** Commercially available rapid assays are quite expensive but give results within 30 minutes and are therefore useful in field conditions. These are as follows:

- a. **The Biostar Chlamydia OIA** (Biostar, Inc., Boulder, Colo.): It is an optical immunoassay that provides test results in less than 30 min, using a test format that allows office-based testing. Compared to all conventional assays, the sensitivity of this test is 73.8%.<sup>179</sup>
- b. **Sure cell Chlamydia test:** The test may be carried out on cervical or urethral smears, urine and ocular specimens. It detects *chlamydia* species-specific lipopolysaccharide on a membrane, utilizing immunoperoxidase technique.<sup>171</sup>
- c. **Clear view Chlamydia test.** This test utilizes a portable antigen capture technique using a membrane-based diffusion card and is done only on endocervical specimens. It consists of colored latex particles combined with monoclonal *chlamydia* antibody to detect antigen in the specimens. It is less sensitive than culture, but specificity is high.<sup>180,181</sup>
- d. **Chlamydia rapid test**<sup>182</sup>: It is based on a monoclonal antibody to *chlamydia* lipopolysaccharide coated on a test strip, using SOVS specimens in women. The test provides results in 30 minutes. Compared with PCR and SDA, it is highly specific with high NPV, but sensitivity is less than both the tests. The test is a potentially cost effective alternative to NAATs for diagnosis and may be used as a screening tool for *chlamydia* infection.

### DNA Investigation

**DNA Probe** PACE test utilizes a non-isotopic DNA probe for the detection of specific rRNA of *C. trachomatis* in endocervical and urethral specimens.<sup>183</sup> It compares very well with DFA and the best EIAs. Subsequently, PACE 2 has been found to have sensitivity and specificity as good as EIAs and culture<sup>184–186</sup> or even better than culture.<sup>187</sup> Specimens are not adversely affected by heat or extended transit time during postal transport.<sup>188</sup>

**PCR** DNA amplification assays are superior to standard immunoassays for the diagnosis of *C. trachomatis* infections in urine samples. The common cryptic plasmid is the best amplification target.<sup>189</sup> PCR is more sensitive than culture (99% vs. 78%) with a specificity above 99%.<sup>190,191</sup> The sensitivity of a commercial kit (Amplicor Roche)<sup>191,192</sup> in male urine and female cervical specimens is approximately 20% higher than culture and antigen detection methods.<sup>192</sup> It involves PCR and DNA probe hybridization followed by final detection of PCR product by EIA.

Amplicor *C. trachomatis*/*N. gonorrhoeae* M-PCR assay provides a highly sensitive, specific and robust method for the diagnosis of both *C. trachomatis* and *N. gonorrhoeae* for the early detection of both symptomatic and asymptomatic individuals<sup>140</sup> from urethral and endocervical swabs and urine. Mailed SOVS are convenient and useful for PCR testing for genital *C. trachomatis* infection.<sup>193</sup> In resource-limited settings, pooling of urogenital specimens to detect *C. trachomatis* and *N. gonorrhoeae* by PCR is a simple, accurate, and cost-effective procedure.<sup>145</sup> A new automated Abbott M-RT *C. trachomatis*/*N. gonorrhoeae* PCR assay is also available as an alternative.<sup>194</sup>

**Ligase Chain Reaction (LCR)** This extremely sensitive and specific rapid test, utilizing a single swab and requiring convenient room temperature storage and transport of specimens, is better than culture and DFA.<sup>195,196</sup> The test is highly sensitive in detection of chlamydia urethritis as well as asymptomatic infections in FVU in men.<sup>196</sup> As mentioned earlier, the pooling of urine samples in women is sensitive, specific, and cost saving.<sup>151</sup>

**Transcription-Mediated Amplification (TMA) and Hybridization Protection Assay** Gen Probe Amplified *C. trachomatis* assay (TMA) detects *C. trachomatis* ribosomal RNA (rRNA) in endocervical and urinary specimens.<sup>197</sup> Its sensitivity and specificity are similar to culture using urine and urethral and endocervical swabs.<sup>198</sup> The APTIMA TMA assay for *C. trachomatis* and *N. gonorrhoeae* has the greatest sensitivity of all the commercial NAATs carried out in non-invasive samples containing small amounts of nucleic acid. Vulvovaginal swabs appear to be the specimen of choice in women and FVU in men.<sup>199</sup>

**Strand Displacement Amplification (SDA)** PCR, SDA, and LCR show comparable high sensitivities on single dry endocervical swab specimens from female commercial sex workers for detection of both *N. gonorrhoeae* and *C. trachomatis*. Probetec ET SDA is the only NAAT showing 100% specificity for both the infections.<sup>200</sup> In contrast, according to a later study,<sup>201</sup> the specificity is excellent,



but the sensitivity of SDA is significantly lower than that of other molecular techniques.

The sensitivity for three amplified probe assays, BDProbeTec™ (BD Biosciences, Sparks, MD); Abbott LCx®, (Abbott Diagnostics, Abbott Park, IL); Roche COBAS AMPLICOR® (Roche Diagnostic Systems, Indianapolis, IN) for detection of *C. trachomatis* using swab and urine are comparable, with the exception of COBAS AMPLICOR carried out in urine specimens from females.<sup>202</sup> The specificity for all the assays are very high.

#### Q-Beta Replicase Amplified Hybridization Assay (Gen Trak Inc.):

Although the lower limit of detection of *C. trachomatis* rRNA by this novel assay and a semi-quantitative PCR is five elementary bodies, the test is comparable to PCR.<sup>203</sup>

#### Isolation in Tissue Culture

Irradiated or cycloheximide-treated McCoy cells, BHK-21, Hela-229 have been used successfully for the isolation of *C. trachomatis*.<sup>204,205</sup> Confirmation of the isolates is done either by Giemsa or iodine stains (Fig. 26.10). Fluorescein-labeled monoclonal antibodies<sup>206</sup> can rapidly confirm the presence of inclusion bodies 48 hours after incubation (Fig. 26.11). The cell culture is not 100% sensitive, therefore the gold standard for diagnosis is expanded by using multiple non-culture tests mentioned above to identify infected specimens missed by culture.<sup>207</sup>

#### Serology

Several serological tests for the detection of IgG or IgM antibodies are available commercially. However 45–65% of patients may have antibodies as a consequence of past infection and the traditional approach for the detection of four-fold rise in titer does not seem to be applicable. Detection of antibodies may be particularly useful for the diagnosis of upper genital tract infections, especially in cases of *C. trachomatis* associated tubal factor infertility,<sup>208</sup> as these infections may not be detected by endocervical culture. Elevated titers are detected by EIA or CF and/or micro-immunofluorescence (MIF) techniques.

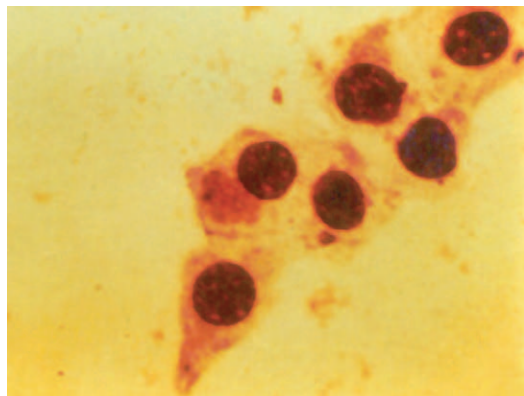


Fig. 26.10: Iodine-stained inclusion body of *C. trachomatis* in McCoy cell culture.

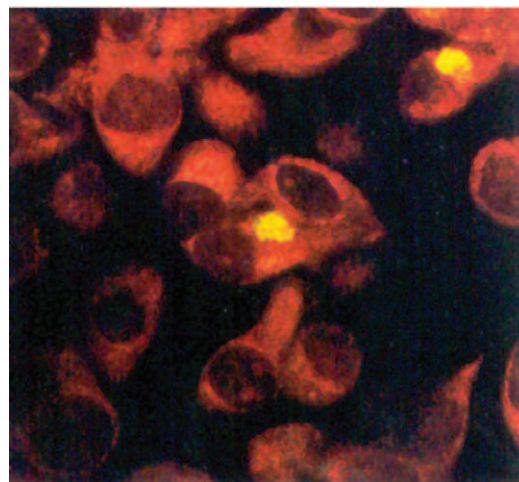


Fig. 26.11: McCoy cells with fluorescent antibody stained *C. trachomatis* inclusions (high power). Courtesy: Aruna Mittal, New Delhi, India.

Interpretation must be done carefully. A single whole antigen inclusion test is capable of detecting antibodies to a group antigen as well as type-specific antibodies to *C. trachomatis*.

The detection of IgM antibodies may also be helpful in establishing acute chlamydia infections of the genital tract and the test is sensitive and specific.<sup>209</sup> Detection of IgG and IgM antibodies are valuable for epidemiological studies.

Serologic classification has been reorganized from 15 serovars to 10 immuno-types. Four antigenic pools or complexes of *C. trachomatis*, e.g. C, D, G, F, and K complexes are recognized. Using MIF, when a specific IgM response to a different pool of *C. trachomatis* immuno-type is observed, new infections can be detected in patients who have had previous infections with other immuno-types.<sup>210</sup>

#### Lymphogranuloma Venereum (LGV)

Serological tests using the CFT or MIF are also useful in the diagnosis of LGV. Usually a MIF titer of  $\geq 256$  and CF titer  $\geq 64$  are reported to indicate acute infection.<sup>211</sup> Recently, RT-quadruplex PCR assay capable of detecting LGV, non-LGV or mixed infections simultaneously in rectal specimens, has been developed.<sup>212</sup>

#### MYCOPLASMA SPECIES AND UREAPLASMA UREALYTICUM

Mycoplasmas are the smallest free-living organisms, widespread in nature. They are prokaryotes but lack a cell wall. However, they have a unique cell membrane that contains sterols, which are not present in either bacteria or viruses.<sup>213</sup> Several mycoplasma species have been isolated from humans, of which *Mycoplasma hominis* (*M. hominis*), *Ureaplasma urealyticum* (*U. urealyticum*), and *Mycoplasma genitalium* (*M. genitalium*) colonize the genital tract. Although the role of *M. hominis* in the pathogenesis of genital infections is unclear, it has been associated with infections

in women such as pyelonephritis, PID, and post-partum fever with stillbirth.<sup>214</sup> *U. urealyticum* has been reported as a causal agent of acute urethral syndrome in women<sup>215</sup> and with reproductive failure. This organism may also be an etiological agent for NGU in men.<sup>216</sup> A large number of sexually active males without urethritis are asymptotically colonized with both species. *M. genitalium* behaves similarly to *C. trachomatis* and carriage of these two organisms may be independent of one another.<sup>212</sup> *M. genitalium* is known to cause non-chlamydial NGU in men and to be associated with PID, endometritis, and possibly preterm birth in women.<sup>216,217</sup> There is a strong association between *M. genitalium* and HIV infections.<sup>218</sup>

## Laboratory Diagnosis

**Collection and transport of specimens:** The specimens which may be used for the isolation of *Mycoplasma* or *Ureaplasma* from the genital tract are urethral swabs, urine (with or without massage of prostate and para urethral glands) or semen in men, and high vaginal or cervical swabs, and purulent aspirate from salpinges (in non-bacterial salpingitis cases) in women.

These are collected on rayon-tipped swabs on a thin wire, as certain wooden sticks may be toxic to *Mycoplasma*. Contact with antiseptics, analgesics or lubricants should be avoided.<sup>219</sup> The urethral and cervical swabs are collected as described for *chlamydia*. To preserve viability up to 24 hours, the swabs should be placed immediately in transport media such as (i) *Mycoplasma* broth without inhibitors, (ii) Stuart's transport medium, (iii) ordinary nutrient broth with horse serum, (iv) SP-transport medium containing 10% heat inactivated fetal calf serum without antibiotics,<sup>220</sup> (v) trypticase soyabroth with 0.5% albumin and 400 µ/ml penicillin.

If immediate plating is not possible, samples should be stored at +4°C and sent to the laboratory within 24 hours or frozen at -70°C in media containing protein. Endocervical swab specimens transported in FVU demonstrated higher sensitivity by RT-PCR than FVU specimens only and endocervical swab specimens transported in 2-SP medium, for detection of *M. genitalium* DNA.<sup>221</sup>

## Laboratory Methods

Direct non-culture techniques.

### Leukocyte Esterase (LE) in FVU and Presence of Leukocytes in Urethral and Cervical Smears

This combination has been used to screen patients prior to specific *M. genitalium* testing, but about 10% of infected individuals remain undetected.<sup>222</sup>

### DNA Investigation

**PCR** Specific and sensitive methods are needed for identification of *M. genitalium* as it is difficult to culture the organism from patient samples.<sup>223</sup> Compared to culture, a M-PCR for the

detection of *U. urealyticum*, *M. genitalium*, and *M. hominis* in a single amplification reaction is less sensitive, but has similar specificity. The test offers a rapid, sensitive, and easy method to detect genital mycoplasmas.<sup>224</sup> The increased sensitivity and shorter time requirement of PCR support its further development for the diagnosis of *U. urealyticum* infection.<sup>225</sup>

Good correlation is seen between a quantitative RT-LightCycler PCR and conventional 16S rRNA gene PCR assay for *M. genitalium* to determine the bacterial load in patients' specimens.<sup>226</sup> The RT-*M. genitalium* adhesin protein (MgPa) gene PCR is well-suited for the diagnosis of *M. genitalium*.<sup>227</sup> A M-PCR-based reverse line blot (mPCR/RLB) assay developed to detect 14 urogenital pathogens including *U. urealyticum*, *M. hominis*, and *M. genitalium* is accurate, convenient, and inexpensive for the detection of multiple potential pathogens in FVU specimens from men.<sup>100</sup>

**TMA** A newly developed research-only TMA (Gen-Probe Incorporated) compared to an in-house DNA-based PCR assay for detection of *M. genitalium* is highly specific and vaginal swab specimens are the most sensitive specimen type in women.<sup>228</sup>

## Isolation

**Culture Media and Method of Inoculation** The inoculated plates and broths are incubated under microaerophilic (95% N<sub>2</sub> + 5% CO<sub>2</sub>) or anaerobic conditions in plastic boxes or in glass jars with sealed lids with a roll of cotton wool soaked in water to maintain humidity.<sup>224</sup> For the isolation of *Mycoplasma* in samples from the lower genital tract, 10-fold dilutions of the specimen<sup>229</sup> are used to distinguish the number of organisms likely to represent an active infection (>10<sup>4</sup>–10<sup>5</sup>/ml) from those of a chronic low-level carriage. Ten-fold dilutions of swab eluate are either spread on standard *Ureaplasma* media or into biphasic media without methylene blue as well as into liquid *Ureaplasma* medium. Serial dilution also dilutes antibodies, antibiotics and other inhibitors present in the specimen. The media commonly used are PPLO broth and agar, Shepherd A-7B and New York City Agar.<sup>230</sup> SP4 medium has been used successfully for the isolation of *M. hominis*. Any color change within 24–48 hours in liquid medium due to metabolic activities may indicate growth and is sub-cultured immediately in PPLO agar.

## Colony Characteristics and their Identification

- (i) *M. hominis* colonies are about 200–300 µm and have classical fried egg appearance. These are stained with Dienes stain by placing a small block of the agar plate on a glass slide and covering the colony with the stain. A coverslip is added and examined microscopically under low power. The periphery of the colonies stains light blue and the centre, dark blue. *M. hominis* requires only 2 days forming colonies and producing alkaline color change without turbidity in medium containing arginine.
- (ii) *M. genitalium* colonies are much smaller, many times devoid of typical appearance and are very difficult to recover from culture, requiring 2–3 months of incubation.



(iii) *Ureaplasma* colonies, once called T-strain *Mycoplasma*, are extremely small (10–30  $\mu\text{m}$ ) and difficult to see with the naked eye. A stereoscopic microscope should be used for the identification of colonies. They do not have the fried egg appearance typical of *Mycoplasma* colonies. They are identified by their (i) ability to split urea, (ii) inhibition by erythromycin, and (iii) resistance to lincomycin. Urease activity of *Ureaplasma* may be detected on solid agar containing urea and manganese sulfate or calcium chloride.<sup>230</sup> The urea containing broth medium with the growth that has just changed color is sub-cultured on agar medium containing urea buffer and a sensitive ammonia indicator. Urea positive colonies are large and dark golden brown in color because of deposition of manganese dioxide.

A *Mycoplasma* Duo kit<sup>231</sup> shows a significantly higher detection rate than a conventional culture using A7 differential agar for the detection of *M. hominis* and *U. urealyticum*. Detection of the mycoplasmas is based on the specific metabolic properties of each organism to hydrolyze either arginine or urea.

**Serologic identification:** Due to the presence of several serotypes of *U. urealyticum*, serologic identification is difficult. However, simple typing techniques based on agar growth inhibitions,<sup>232</sup> have been reported. An EIA for serotyping *Ureaplasma urealyticum* strains using monoclonal antibodies has been reported.<sup>233</sup>

**Identification by DNA techniques:** The colonies may be detected by using PCR with genus specific primers and probes, or amplification of the 16S RNA gene and sequencing of the product. For PCR, a similar method of dilution as described in culture should be used.<sup>234</sup>

**Culture of *M. genitalium*:** An improvement of the Vero cell culture method in which the growth is monitored by quantitative RT-PCR has been reported. The complete isolation procedure from the initial inoculation to completion of single-colony cloning takes about 1 year.<sup>235</sup>

### Serology

Serological tests, including EIA, have been used to detect antibody levels against *M. hominis* and *M. genitalium* in women with salpingitis and post-partum fever.<sup>236</sup> In patients with NGU, an EIA employing cell lysate *Ureaplasma* antigen<sup>237</sup> could detect a *Ureaplasma* antibody response. The test is also positive in *Ureaplasma* negative subjects, 10% by IgG and 7.5% by IgM. Similarly in tubal infertility cases, antibodies to *U. urealyticum*<sup>238</sup> and *M. hominis*<sup>238,239</sup> were detected by EIA.

## VAGINITIS

### Candidiasis

Millions of women all over the world suffer from vulvovaginal candidosis (VVC), and symptomatic or asymptomatic infections are common. Clinical signs and symptoms are non-specific and clinical diagnosis is often not possible.

The most common etiological agent of VVC is *Candida albicans* (*C. albicans*) (85%), followed by *C. glabrata*, *C. tropicalis*, *C. krusei*, and other *Candida* species.<sup>240</sup> Non-*albicans* species produce VVC clinically indistinguishable from that produced by *C. albicans*.<sup>241</sup> The organisms are also found in about 7.2% of asymptomatic women as normal flora.<sup>240</sup> Colonization of *Candida* in the vagina occurs under certain conditions including normal physiological reproductive hormonal changes in women, diabetes mellitus and the use of broad-spectrum antibiotics.<sup>242</sup>

Although not a traditional STI, *Candida* may be sexually transmitted to male partners and cause balanitis, balanoposthitis, and NGU. Colonization of penis by *Candida* has been reported in approximately 20% of male partners of women with recurrent VVC.<sup>243</sup> Incidence of *C. glabrata*, *C. tropicalis*, and *C. parapsilosis* among HIV-positive patients has increased,<sup>244</sup> but VVC is not in itself a sentinel feature of HIV infection.<sup>245</sup>

Clinical features of VVC are non-specific, and the standard laboratory test to identify *Candida* organisms from a vaginal swab may take between 5 and 7 days. Simple, reliable and rapid diagnostic tests are not available and as many as half the women with VVC are misdiagnosed, resulting in over treatment with antifungal agents.<sup>246</sup> In diagnosing VVC, clinical findings, microscopic examination and vaginal culture results should be correlated.

### Laboratory Diagnosis

**Collection and transport of specimens:** Using a speculum, a vaginal swab is collected, preferably with a polyester swab, from the posterior fornix.<sup>247</sup> The skin surrounding the genitals is also rubbed. In men, the swab is moistened with saline and the glans is rubbed. The swabs should be sent to the laboratory, as soon as possible, to prevent drying. *C. albicans* can survive for 24 hours on a moist swab. However, the use of a transport medium is recommended.<sup>240</sup>

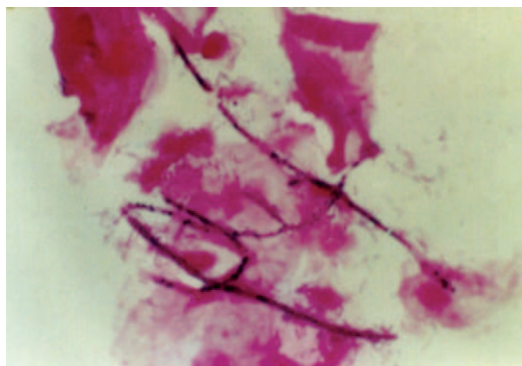
### Laboratory Methods

Direct non-culture tests.

**Microscopy** The specimen is placed on a glass slide with a drop of saline (if required), covered with a coverslip and examined under the high power (40 $\times$ ) lens. Budding cells and long pseudohyphae are the typical findings. The specimen can also be examined in 20% KOH preparation or in a Gram-stained smear (Fig. 26.12). The microscopic demonstration of budding cells and pseudomycelia is not confirmatory, but is suggestive of candidosis. Direct microscopy may be negative in 50% of the patients with culture positive symptomatic VVC.<sup>248</sup> *Candida* are found in tissues as yeast cells (small oval cells with budding).

**Antigen Detection** EIA to detect yeast mannan, with a sensitivity of 0.1 ng/ml, may be useful for diagnosis in cases of systemic candidosis.<sup>249</sup>

**Isolation** Although culture is the most sensitive method for the diagnosis of VVC, a positive culture does not necessarily indicate that the *Candida* isolated is responsible for the symptoms.

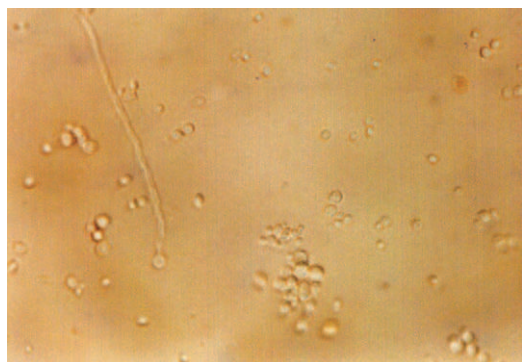


**Fig. 26.12:** Gram-stained smear of vaginal fluid showing *Candida* budding cells and pseudohyphae.

The swab is inoculated into tubes containing Sabouraud's dextrose agar (SDA) with antibiotics (chloramphenicol or gentamycin). Typical smooth, opaque, white to creamy, glistening colonies of *Candida* develop on incubating the tubes at 37°C for 48 hours.<sup>247</sup> A wet mount examination confirms the presence of yeast cells. Recently, commercial media containing chromogenic substrates were found to have better detection rates than SDA.<sup>250</sup> Use of cycloheximide prevents the growth of *Candida* species other than *C. albicans*.<sup>247</sup>

**Speciation-Germ Tube Test** This is a simple, rapid, and frequently used test for the identification of *C. albicans*.<sup>242</sup> A colony of *Candida* is emulsified in 0.5 ml of bovine/horse/human serum and incubated at 37°C for 2–3 hours. *C. albicans* produces short lateral hyphal filaments or germ tubes that are not constricted below the blastoconidium (Fig. 26.13). Other yeasts either do not produce germ tubes, take a longer time to do so or produce them with constrictions. *C. albicans* may be identified by production of chlamydoconidia in cornmeal agar.<sup>247</sup> Identification of other yeasts requires extensive biochemical test systems, available commercially.<sup>247</sup> Complete speciation is desirable because of variations in pathogenicity and drug susceptibility of different species.

**Serological Tests—EIA** A new EIA (SysCan3 *Candida* Pathology ELISA Kit, Rockey Biomed Ltd., Perth, Australia) for anti-



**Fig. 26.13:** Germ tube test for confirmation of *C. albicans* colonies.

*Candida* antibodies demonstrated a sensitivity of 78% and a specificity of 90%, compared to vaginal cultures in sexually active females infected with VVC. The semi-quantitative nature of the test may also allow monitoring of the progression of VVC.<sup>246</sup>

There is a need for a rapid, inexpensive, reliable, POC test to increase the diagnostic accuracy for successful treatment of genital candidosis. Ongoing concerns in management of VVC include vaginal acquisition of non-*albicans Candida* species and the development of antimycotic drug resistance in *C. albicans* vaginal isolates.<sup>245</sup>

## Trichomoniasis

Trichomonal vaginitis is a common parasitic STI caused by a protozoa, *Trichomonas vaginalis* (*T. vaginalis*).<sup>251</sup> The discharge is greenish grey and foul smelling. It remains asymptomatic in 50% of infected women but can cause vaginitis, cervicitis, preterm labor, urethritis, and prostatitis.<sup>252</sup> The infections in men are characterized as NGU, epididymitis, balanoposthitis, urethral stricture and infertility,<sup>253</sup> but most have a sub-clinical infection.<sup>251</sup> Vaginal trichomoniasis has been associated with HIV acquisition.<sup>254</sup>

## Laboratory Diagnosis

**Collection of specimen:** Under speculum examination, using a sterile swab or bacteriological loop, the sample is collected from the posterior vaginal fornix. In case of delay in reaching the laboratory, the specimen may be placed in transport media, e.g. Whittington medium/Kupferberg medium, in which the trichomonads survive for 24 hours. In men, the urethra is sampled with a cotton-wool swab or preferably a polyester swab. Centrifuged urine deposit is also a good specimen for the detection and isolation of *T. vaginalis*.

## Laboratory Methods

Direct non-culture tests.

**Wet Mount** This is a simple diagnostic procedure followed in the clinic. In a wet preparation, examined at 40× magnification, the protozoa can be identified by their typical jerky motility and are seen along with PMNL. *T. vaginalis* is an ovoid globular pear-shaped flagellate 12.25–15 µm long,<sup>255</sup> slightly bigger than PMNL. It has got four free anterior flagella and one extraposterior flagella attached to an undulating membrane extending along the length of the body and showing typical motility. DF microscopy can reveal the individual flagella and undulating membrane. Mixed infections with *Candida* or micro-organisms responsible for bacterial vaginosis are commonly seen. The wet mount reveals trichomonads in only 40–80% of cases<sup>256,257</sup> because of faulty specimen preparation, failure of immediate examination and presence of other microbes. Negative wet mount does not exclude the infection.

**PAP Stain/Giemsa (Fig. 26.14)** These methods have poor sensitivity and specificity and are not useful for routine laboratory diagnosis.

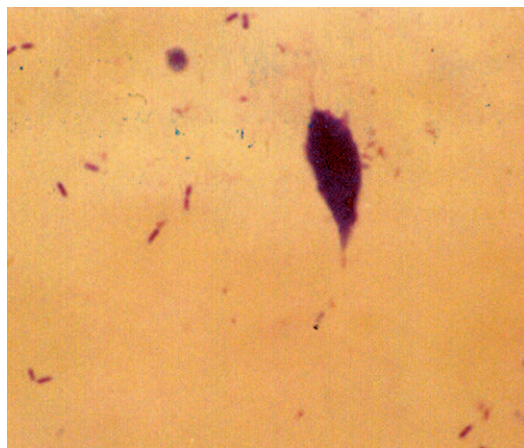


Fig. 26.14: Morphology of *T. vaginalis*—Giemsa stain.

**Detection of Antigen** (i) **Latex agglutination:** Taking the culture in Diamond medium as the gold standard, the latex technique carried out on vaginal discharge is more sensitive and efficient, and has a higher predictive value than the direct wet mount examination. It provides the diagnosis in approximately 3 minutes and due to its simplicity it may be carried out by the paramedical personnel in order to offer specific treatment on the same day.<sup>258</sup> (ii) **Dot-immunobinding assay (DIBA) with monoclonal antibody:** DIBA is as sensitive as the wet mount but less sensitive than culture.<sup>259</sup>

**DNA Investigation** (i) **DNA probe:** A multiplex probe assay for *T. vaginalis* and *Gardnerella vaginalis* (*G. vaginalis*), compared with wet mount and culture in Diamond's medium, is highly sensitive and specific.<sup>260</sup> (ii) **PCR:** Compared to culture, the sensitivity, and specificity of PCR, using vaginal samples, are quite good but with urine, the sensitivity is less. It is an alternative to culture<sup>260</sup> but exclusive use of urine-based detection is not appropriate in women. (iii) **PCR EIA:** In the absence of vaginal specimens and when culture is not feasible, urine-based PCR-EIA may be useful for the detection of trichomoniasis in both sexes.<sup>261,262</sup> It is highly sensitive (98%) for detection of *T. vaginalis* in male partners of women with trichomoniasis. Even with this test, reliable detection of *T. vaginalis* in males requires multiple specimens. The study emphasizes the importance of partner evaluation and treatment as most of the male partners of infected women are infected.<sup>263</sup> (iv) **RT-PCR (Fluorescence resonance energy transfer [FRET] probe chemistry):** FRET-based assays can provide rapid, accurate, and high-throughput detection of *T. vaginalis* and may prove useful for large-scale screening programmes.<sup>264</sup> (v) **TMA assay:** TMA assay and FRET PCR for *T. vaginalis*, in clinical samples from men (urine) and women (SOVS), showed high sensitivity and specificity.<sup>265,266</sup>

**Isolation** Culture of *T. vaginalis*, the gold standard test,<sup>255</sup> is more sensitive than the direct wet mount and detects the parasite from vaginal and urethral swabs, urine sediment or prostatic fluid. Culture is usually done in reference laboratories and is especially

useful when relatively few organisms are present. A variety of liquid and semi-solid media, like modified Diamond, Feinberg, Whittington, Trichosel, Hollander, and Kupferberg medium are used. Optimal *in vitro* growth occurs in moderately anaerobic conditions and consequently the organism will grow best at the depth of culture tubes filled with the medium. The growth appears usually in about 2–4 days, but should be examined till 7 days before discarding.<sup>267</sup> Studies suggest that modified Diamond's medium allows for prolific growth and is more suitable than Kupferberg medium.<sup>267</sup>

The *In pouch* TV test has a specimen transport vessel, growth chamber for incubation and a viewing chamber for microscopy. The reported shelf life is 15 months. The medium contains antibacterial and antifungal agents. After inoculation, the medium is incubated at 37°C for 24–48 hours and up to 5 days for positive growth. Compared with the other media used commonly in laboratories, the sensitivity is higher and it does not require opening for viewing.<sup>268,269</sup>

## Bacterial Vaginosis

Bacterial vaginosis (BV) is a polymicrobial condition characterized by a malodorous vaginal discharge associated with the presence of *Gardnerella vaginalis* (*G. vaginalis*), *Prevotella* sp. (formerly *Bacteroides* sp.), and other anaerobic bacteria such as *Peptostreptococcus* sp., *Porphyromonas* sp., *Mobiluncus* sp., and *M. hominis*.<sup>270</sup> The predominant microorganisms present in the healthy vagina are facultative anaerobic lactobacilli, earlier recognized as acidophilic,<sup>271</sup> but later as hydrogen peroxide producing.<sup>272</sup> *G. vaginalis* may be present in the healthy vagina without producing vaginal discharge.<sup>273</sup> Several gynecological and obstetric complications of BV in women are reported and BV was significantly associated with HIV seropositivity among a group of commercial sex workers in Thailand.<sup>274</sup>

## Diagnosis

The diagnosis is usually based on the presence of three of the four following characteristics in the absence of a sexually transmitted infection:

- (i) Homogeneous, grayish-white, thin, adherent vaginal discharge.
- (ii) Vaginal fluid pH of >4.5.
- (iii) Intensification of fishy odor from the discharge, on addition of 10% KOH.
- (iv) Presence of clue cells (usually representing at least 20% of vaginal epithelial cells) on microscopic examination of direct KOH mount.

**pH Test** The specimen collected from the lateral or posterior fornix is touched directly on the paper pH indicator strips (3.8–6.0). Alternatively, the pH paper can be touched on the speculum after it is withdrawn. The test is highly sensitive, but gives FP results if the specimen is contaminated with cervical mucus, semen, *T. vaginalis* infected sample or menstrual blood.<sup>275</sup>



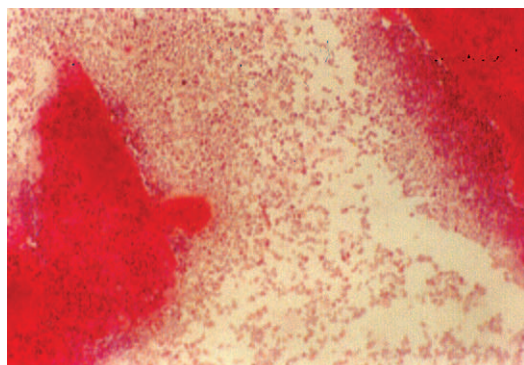
**Amine Test (Sniff Test)** Women with BV complain of foul vaginal smell because anaerobic bacteria present in the vagina decarboxylate amino acids lysine to cadaverine and arginine to putrescine. These amines become volatile in the presence of potassium hydroxide (KOH) and produce the typical fishy odor. After a positive reaction, a specimen quickly becomes odorless upon standing as the amines rapidly volatilize completely. The test is least sensitive but the most specific single predictor.<sup>273,275</sup>

### Laboratory Methods

**Direct Microscopy** (i) **KOH mount:** A drop of vaginal fluid is mixed with a drop of 10% KOH on a glass slide, covered with a cover slip and examined under high power (40×) of microscope for clue cells. These are squamous epithelial cells studded with many small coccobacilli obscuring the edges, resulting in a stippled granular appearance of the cells. In most patients with BV, a mixture of normal exfoliated vaginal epithelial cells and more than 20% clue cells are seen.<sup>275</sup> (ii) **Gram-stained smear:** The examination of Gram-stained smear is superior to wet mount and reveals the characteristic morphology of the bacteria<sup>276,277</sup> and clue cells (Fig 26.15). Quantitative estimation of the type of bacteria can also be done. Normal vaginal flora consists of predominantly lactobacilli, which are thick gram-positive bacilli and are replaced by anaerobic bacteria and *G. vaginalis* in BV. Gram-stained smears on microscopic examination can be classified into four grades:

- Presence of only lactobacilli.
- Mixed flora, predominantly lactobacilli with few coccobacillary morphotypes.
- Mixed flora, predominantly *Gardnerella* like, anaerobic bacterial morphotypes and a few lactobacilli.
- Mixed flora of gram-positive, gram-negative and gram-variable coccobacilli in the absence of lactobacilli.

A scoring system based on the semi-quantitative assessment of *Lactobacillus* morphotypes, *G. vaginalis*, *Prevotella* sp. Morphotypes, and *Mobiluncus* morphotypes, detecting the shift from predominance of lactobacilli to predominance of *Gardnerella* and other anaerobic organisms has 89% sensitivity and 83% specificity for diagnosis in comparison with clinical criteria.



**Fig. 26.15:** Gram-stained smear of vaginal fluid showing "clue cells."

A score of 7–10 is considered diagnostic of BV.<sup>277</sup> This method has good inter-centre reproducibility.<sup>278</sup> The Ison Hay criteria<sup>279</sup> for diagnosis of BV may be more useful in clinical practice. Culture is not recommended.

## Others

### CONDYLOMA ACUMINATUM (GENITAL WARTS)

Genital infections due to human papilloma viruses (HPV) are becoming one of the most prevalent STIs in the United States.<sup>280</sup> HPVs are double-stranded DNA viruses. Approximately 20 HPV types are known to cause genital or anal lesions.<sup>280</sup> The most common types of genital HPVs are HPV-6, HPV-11, HPV-16, and HPV-18. HPV-16/18 is known to be associated with cervical intraepithelial neoplasia and invasive cancers.<sup>281,282</sup>

The immunological methods are not very useful for detecting the specific HPV types and the virus cannot be cultured. Specific laboratory diagnosis and typing of HPV has been possible with the advancement of molecular biological techniques, like nucleic acid hybridization, and PCR. However, laboratory diagnosis has, at present, not much application in clinical practice.

### Laboratory Diagnosis

**Collection of specimen:** Specimens used for diagnosis are biopsies from tumors and infected tissues and exfoliated epithelial cells, collected with wooden or plastic spatula.<sup>282</sup> Samples from the cervix should be collected from the junction of ecto and endocervix. Out of various genital sites, the penile shaft, glans penis/coronal sulcus, scrotal, perianal or anal samples, semen and urine should be sampled for optimal detection of HPV-DNA by PCR and genotyping.<sup>283</sup> The swab method used to obtain skin exfoliated cells is adequate for sample collection.<sup>284</sup>

Combined sensitivity for HPV-DNA is more than 70% when patients use Dacron swabs, cotton swabs, or cytobrushes to obtain their own vaginal specimens. SOVS may be an appropriate alternative for low resource settings or in patients reluctant to undergo pelvic examinations.<sup>285</sup> Biopsy specimens after collection can be divided into two parts, one part embedded in paraffin wax for antigen detection and *in situ* hybridization and the other suspended in PBS and frozen at  $-70^{\circ}\text{C}$  for DNA tests.<sup>282</sup>

### Laboratory Methods

#### Cytology

HPV infection in epithelium produces CPE, koilocytosis and other cellular irregularities which are detected by PAP smear.<sup>282,286</sup> The method is relatively insensitive to detect asymptomatic infections.



Koilocytes are large cells with an irregular hyperchromatic nucleus and a perinuclear clear ring in the dense cytoplasm. When koilocytosis is not exhibited, specific HPV antibodies, coupled with horse-radish peroxidase (HRP), may be used to stain HPV within infected tissue. An elevated number of koilocytes, > 8 per HPE, may suggest the possibility of HIV infection.<sup>286</sup> A diagnostic pathway, integrating liquid-based cytology, computer-assisted interpretation, and HPV DNA testing to screen for cervical cell changes, has potential to improve primary screening of women at risk and is cost effective.<sup>287</sup>

### Detection of Antigen

Commercial kits for the detection of HPV antigens by IF, EIA or DIP utilizing monoclonal antibodies raised against bovine papilloma viruses and labeled with fluorescein isothiocyanate, HRP or alkaline phosphatase, respectively, are available but their sensitivity and specificity are quite low.<sup>288</sup>

### DNA Tests

**Southern Blot (SB) Hybridization** This is the gold standard test for the detection of HPV DNA, utilizing radioactive or non-radioactive labeled probes.<sup>289</sup> Using penile swabs and cervical biopsy specimens, two commercial kits,<sup>290</sup> one utilizing SB and the other a viral type dot blot, are useful in differentiating positives and negatives. The second kit can also differentiate HPV types.

**Filter in situ Hybridization** It detects HPV directly in cells from cervical scrapings<sup>291</sup> and tissue sections. FP reactions have been reported.

**Dot Blot Hybridization** The test with optimum sensitivity and specificity is available for detection of HPV,<sup>292</sup> but is primarily a research tool.

**PCR** This test, amplifying specific target DNA sequences, is more sensitive than hybrid capture.<sup>293,294</sup> Biopsy tissues, genital swabs, saliva, and urine have shown positive HPV PCR. It can detect 10–100 copies of the viral genome, as compared to the conventional methods, detecting  $10^5$ – $10^6$  copies.<sup>295</sup> An in house and a commercial PCR for detection of HPV types 16 and 18 and a commercial M-PCR for HPV types 6, 11, 16, 18, and 33 were tested in paired urine and cervical samples of women with abnormal cytology. A higher urine/cervix HPV detection sensitivity in cancer and high-grade lesions suggests that urine testing may be done to detect HPV when these lesions are present.<sup>296</sup>

In a recent study, QRT-PCR had a higher detection rate for HPV-16 than conventional PCR in cervical, SOVS and urine specimens in women. The HPV viral load in all three sampling sites correlated with the severity of disease, determined by histology.<sup>297</sup>

**Genotyping** Due to the differences in the oncogenic activity of HPV, it is clinically important to accurately identify HPV types in a simple and time effective manner. A PCR-restriction fragment length polymorphism (PCR-RFLP) method allows

discrimination of individual mucosal HPV types in single/multiple infections.<sup>298</sup>

### VIRAL HEPATITIS

The diseases caused by hepatitis A, B, C, D, and E viruses are extremely common and pose a considerable disease burden in both developing and developed countries. Some of them, especially hepatitis C (HCV) and to some extent hepatitis B (HBV) produce persistent infection. In addition to blood transfusion, sexual acquisition and transmission can occur. Screening for these infections may be appropriate in some patients with STIs.

### Laboratory Techniques

The laboratory diagnosis is mainly based on serology. EIA for detection of all the important markers are available.

#### Hepatitis A

It is usually diagnosed by EIA. During the acute stage, IgM EIA is positive. The infection is not persistent.

#### Hepatitis B (HBV)

The virus has got several serological markers. The markers used to screen patients are HBsAg, which signifies current acute or chronic infection, HBeAg, indicating infectivity of the patients, and anti-HBc IgM, signifying past or present infection.<sup>299,300</sup>

**HBV Surface Antigen (HBsAg)** It is produced by HBV, protein in nature, and is the earliest indicator of acute hepatitis B infection. It frequently identifies infected people before symptoms appear and disappears from the blood during the recovery period. In extremes of age or in those patients with immunodeficiency, such as in AIDS, chronic infection with HBV may occur, and HBsAg remains positive. A positive (or reactive) result indicates an active infection but does not indicate whether the virus can be transmitted to others. A negative result indicates that a person has never been exposed to the virus or has recovered from acute hepatitis and has rid themselves of the virus (or has, at most, an occult infection).

**HBV Surface Antibody (Anti-HBs)** Its presence indicates previous exposure to HBV (but the virus has disappeared and the person cannot transmit it to others) or the person is vaccinated. The antibody also protects the body from future HBV infection.

**HBV e-Antigen (HBeAg)** It is a viral protein associated with HBV infections and is found in the blood only when the viruses are also present. It is often used as a marker of infectivity and may also be used to monitor the efficacy of HBV treatment.

**Anti-HBV Core Antibody (Anti-HBc)** It is an antibody to the HBV core antigen and is produced during and after an acute HBV infection. It is usually found in chronic HBV carriers as well as in those who have cleared the virus, and usually persists for life. Anti-HBc testing is either specific for the IgM antibody (anti-HBc, IgM), indicating acute infection or measuring total

antibody, anti-HBc, indicating past infection, either acute or chronic.

**HBV DNA** It is more sensitive than HBeAg for detecting viruses in the blood stream. It may be used to monitor antiviral therapy in patients with chronic HBV infections. A RT-PCR assay using the LightCycler system combines high sensitivity and reproducibility for HBV DNA quantitation in a high dynamic range of quantitation.<sup>301</sup> The test is much more sensitive than branched-chain DNA (b-DNA) assay for detection of HBV DNA in sera and is useful for early monitoring of HBV load in high-risk patients,<sup>302</sup> detecting HBV DNA levels as low as 100 copies/ml.<sup>303</sup>

### Hepatitis C

Hepatitis C virus (HCV) is a RNA virus which causes almost all cases of parenterally transmitted non-A, non-B viral hepatitis (NANBH). Although most infections become chronic, leading to chronic liver disease, most patients with HCV infection are asymptomatic. The predominant modes of transmission are by blood, blood products or other parenteral exposure, particularly injecting drug use. There is evidence of a small but definite risk of sexual transmission.<sup>304</sup>

Diagnostic tests for hepatitis C<sup>305</sup> are divided into the following two general categories:

- 1) serological assays that detect antibody to hepatitis C virus (anti-HCV); and
- 2) molecular assays that detect, quantify and/or characterize HCV RNA genomes.

Serological assays have been subdivided into (i) screening tests such as the anti-HCV EIA and (ii) supplemental test such as the recombinant immunoblot assay (RIBA). Three generations of anti-HCV EIAs have been developed, and each generation has resulted in an improvement in the sensitivity of detecting anti-HCV. Supplemental anti-HCV tests are designed to resolve FP testing by EIA. However, EIAs do not differentiate between acute, chronic or resolved infection. EIA-3 and RIBA-3 use antigens from the HCV core, non-structural (NS) 3, NS 4, and NS 5 genes. RIBA is a highly specific test.<sup>306</sup>

HCV ribonucleic acid (HCV RNA) tests indicate the presence of viremia, using target amplification techniques and can detect virus within 1–2 weeks of exposure. Results may not be consistent or comparable between different assays.<sup>307</sup> The test is potentially useful for confirming the diagnosis and monitoring the antiviral response to therapy. Q-PCR is the most sensitive test for determining hepatitis C viral load, whereas the b-DNA test appears to be the most precise method.<sup>308</sup>

## HUMAN CYTOMEGALOVIRUS (HCMV) INFECTION

### Laboratory Diagnosis

Testing for HCMV is usually not recommended as a part of routine STD screening because of the high rate of infection in the

community and because HCMV infection is usually asymptomatic. The tests are usually done when patients are having symptoms of suspected HCMV infection. EIA for detection of IgM and IgG antibodies against HCMV are usually used for screening.

### Summary

The continuing epidemic spread of human immunodeficiency viruses (HIV) calls for the early and appropriate management of patients with STIs and their sex partners for the effective prevention of HIV infection. Adequate management of STIs includes an early diagnosis and correct medical treatment, which is dependent on case finding through reliable laboratory procedures.

Though the syndromic approach to STD case management enables healthcare workers to successfully manage more patients with STIs, there are limitations to this approach. However, the approach can be made more specific by the judicious use of laboratory tests. Besides, tests are essential for the diagnosis of asymptomatic patients. The development of new and rapid nucleic acid amplification tests (NAATs) in the last decade and introduction of multiplexing have considerably widened the field of laboratory diagnosis of STIs. Use of non-invasive methods for collection of specimens, like vaginal tampons and first void urine and their transport have been found to be extremely useful for diagnosis, especially for the screening of asymptomatic low prevalence populations. The tests require evaluation in field situations to determine sensitivity and specificity.

The chapter has attempted to cover the conventional tests, the newer advents, especially in the horizon of NAATs and also the rapid POC tests for developing countries for diagnosis of the common STIs. Detailed information regarding the required specimens for each disease and their method of collection have also been provided. This will offer specific treatment for patients without any delay and in turn a step towards the goal to control the scourge of HIV infection.

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# 27

## Rapid Tests for the Detection of Sexually Transmitted Infections

Rosanna W. Peeling

### Introduction

Most sexually transmitted infections (STIs) are asymptomatic, but undetected and untreated infections can lead to serious long-term complications and adverse outcomes for both pregnant women and their fetus or infant. Affordable curative therapy is available for the major bacterial STIs. Screening and early treatment are therefore critical for effective patient management to prevent the development of long-term complications and to prevent onward transmission.

### Need for Rapid Tests in the Management and Control of STIs

The 2004 World Health report shows that unaffordability and inaccessibility are two major reasons why health services fail.<sup>1</sup> This situation is the reality in many countries with a high burden of STIs. For infected individuals with STI symptoms, seeking care requires traveling long distances to reach a laboratory offering STI diagnostic services, and often the services are limited or not of high quality due to limited resources.<sup>2</sup>

For countries with limited STI laboratory services, the World Health Organization (WHO) recommends the use of syndromic management where patients are treated for all the major causes of a particular syndrome.<sup>3</sup> Syndromic management of STIs works well for urethral discharge, pelvic pain, and genital ulcer disease, but evaluations of the WHO flowcharts have shown that the algorithm for vaginal discharge lacks both sensitivity and specificity for the identification of women with *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infection.<sup>4,5</sup> To increase the specificity of syndromic management of vaginal discharge, some control programs added questions about risk behaviors to the algorithm. However, this has resulted in reductions in sensitivity without necessarily increasing specificity as women are not always aware of the risk behaviors of their partners. Most women with vaginal discharge suffer from vaginal infections such as candidiasis, bacterial vaginosis, or trichomoniasis. These vaginal infections can be diagnosed with a microscope using Gram-stained smears or wet preparation of vaginal discharge.

In the absence of microscopy, presumptive treatment with metronidazole for both bacterial vaginosis and trichomoniasis is safe and inexpensive. Unfortunately, such simple rapid tests are not available for the diagnosis of genital gonococcal or chlamydial infections in women in most developing countries. There is a great need for simple, cheap, point-of-care tests for these infections in women to increase the specificity of syndromic management and reduce over-treatment of genital gonococcal and chlamydial infections.<sup>6,7</sup>

### Principles of Rapid Tests for the Detection of STIs

Historically, Gram-stained microscopy, wet prep, pH, the amine or Whiff test, and the Rapid Plasma Reagin (RPR) Venereal Diseases Research Laboratory (VDRL) tests can provide rapid diagnostic results to guide treatment of some bacterial STIs (Table 27.1). However, tests that depend on a source of electricity to operate equipment or require batching or an experienced technician remain of limited utility in many settings in the developing world.

### MICROSCOPY

Gram-stained urethral smear has a sensitivity of 90–95% for the detection of gonorrhea in men, but this method is at best only about 50% sensitive for endocervical smear specimens from women.<sup>8</sup> Fluorescein-conjugated monoclonal antibodies are commercially available for the detection of elementary bodies of *Chlamydia trachomatis* in endocervical smears and the result can be available in less than an hour. This method has a sensitivity of 80–85% and specificity of 99% but requires a skilled and experienced microscopist as the reading is highly subjective.<sup>9</sup>

Dark-field microscopy is used for the detection of motile treponemes from wet preparations of genital ulcer material in primary syphilis. This technique has a moderate sensitivity but requires a skilled microscopist. In recent years, fluorescein-conjugated antibodies against *Treponema pallidum* have become commercially available for more specific identification of the

**Table 27.1:** Rapid Tests for the Detection of STIs

Tests	STIs	Requirements	Comments
<b>Microscopy:</b> 1. Gram stain 2. Dark field 3. Direct fluorescent antibody assay 4. Wet prep (clue cells) 5. Nugent	<i>Neisseria gonorrhoeae</i> <i>Treponema pallidum</i>  <i>Trichomonas vaginalis</i> Candidiasis Bacterial vaginosis Bacterial vaginosis	Electricity	Sensitivity 95% for men but <50% for women
<b>pH</b>	Bacterial vaginosis	None	
<b>Amine (KOH)</b>	Bacterial vaginosis		
<b>Flocculation:</b> 1. RPR 2. VDRL	Syphilis	Electricity to run centrifuge and rotator -microscope	Result not often given the same day because of batching
<b>Immuochromatography strips:</b>	<i>Neisseria gonorrhoeae</i> <i>Chlamydia trachomatis</i> <i>Trichomonas vaginalis</i> Syphilis HIV Human papillomaviruses Herpes simplex viruses	None	
Enzyme detection	Bacterial vaginosis ( <i>Gardnerella spp</i> )	None	

pathogen in primary and secondary syphilis using fluorescent microscopy.

The examination of a wet preparation of vaginal discharge on a microscope slide has a sensitivity of 50–72% for the detection of *Trichomonas vaginalis* compared to nucleic acid amplified tests and is also useful for detection of candidiasis as the morphology of the fungal hyphae is distinctive.<sup>8,10</sup> The presence of clue cells in the wet preparation is suggestive of bacterial vaginosis.<sup>8</sup> Clue cells are epithelial cells of the vagina that are covered with bacteria, giving them a distinctive stippled appearance. Gram-stained smears from a vaginal swab can also be used for the diagnosis of bacterial vaginosis. The Nugent score has been developed to standardize the diagnosis of bacterial vaginosis.<sup>11</sup> It is based on the scoring of three morphological types, large Gram-positive rods of *Lactobacillus spp.*, small Gram-negative or Gram-variable coccobacilli of predominantly *Gardnerella vaginalis* morphotypes, and Gram-negative curved bacilli of predominantly *Mobiluncas spp.* A Nugent score of 7–10, associated with a decrease in *Lactobacilli spp.*, is indicative of bacterial vaginosis.

### AMINE AND pH TESTS

Bacterial vaginosis is also characterized by a fishy odor upon addition of potassium hydroxide to the vaginal discharge (the amine test) and a vaginal pH greater than 4.5. These are simple tests that can be performed easily in a physician's office.

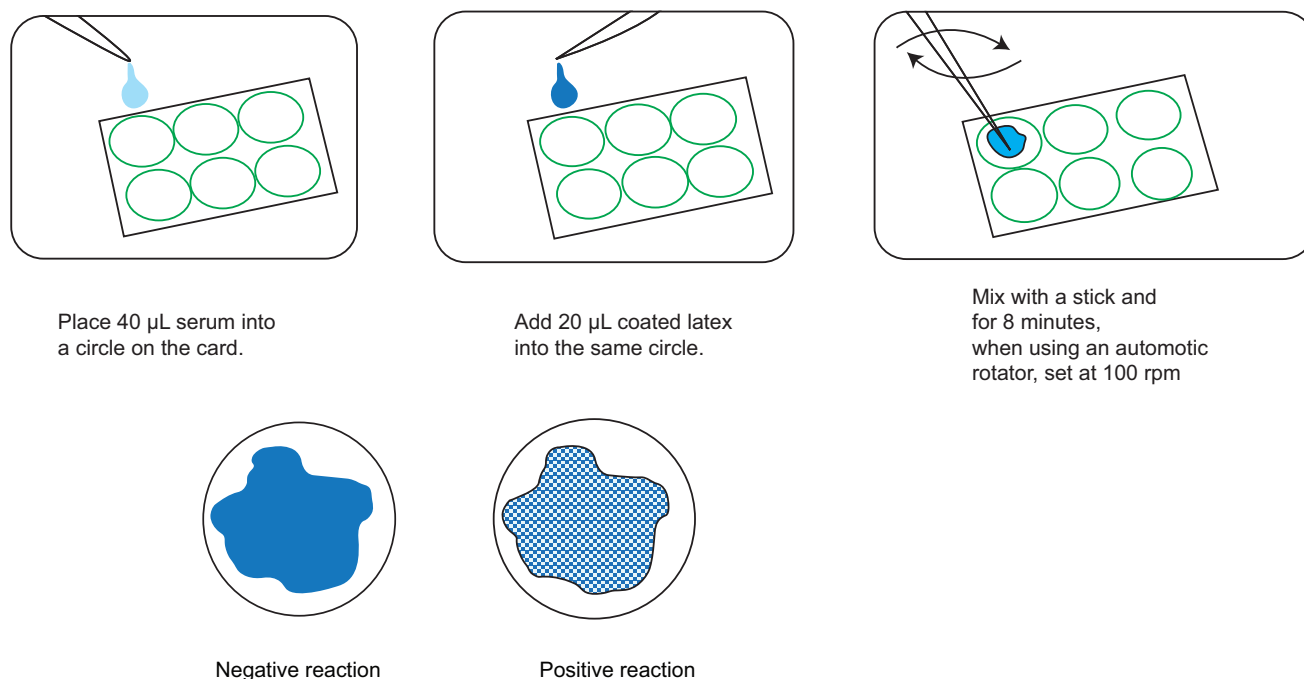
### FLOCCULATION TESTS

The RPR and the VDRL tests are slide flocculation tests used for the diagnosis of syphilis. The tests detect antibodies to cardiolipin, which is a lipoidal antigen extracted from the beef heart. These are non-specific (also known as non-treponemal) assays as it is not known if the antibodies that react with cardiolipin are produced against some lipid component of *Treponema pallidum* or as a result of tissue injury following infection. Biological false positive cases are known to occur with the RPR and VDRL tests, leading to over-treatment. Biological false positive reactions for RPR and VDRL can occur due to pregnancy, malaria, leprosy, viral pneumonia, or immune disorders.<sup>8,12</sup>

The RPR is performed by the addition of serum to a mixture of cardiolipin and charcoal, the resulting mixture is shaken for 8 min. The charcoal particles trapped between the antigen–antibody reaction allow the reader to visualize a grainy pattern that indicates a positive result. The VDRL test is a slide flocculation test, in which the reaction pattern is read under a microscope. The VDRL cardiolipin antigen must be freshly constituted each day of test which limits its utility in peripheral health centers. In recent years, latex particles coated with treponemal antigens are also commercially available for the rapid detection of antibodies for the serodiagnosis of syphilis using the same principle of flocculation (Fig. 27.1).

Test cards are available with circles for six reactions for the latex particle test, 10 for RPR, and 12 wells for the VDRL slide in a single run. Batching saves time and costs but is often why results are not available on the same day to guide treatment.





**Fig. 27.1:** A rapid syphilis test using latex particles coated with treponemal antigen.

### LATERAL FLOW IMMUNOCHROMATOGRAPHIC STRIPS

In recent years, 80–85% of rapid tests are lateral flow immunochromatography test strips (ICTs) which are simple to use without any laboratory equipment, making them suitable for use outside of traditional clinic settings. They can be used for the detection of either antigen or antibody in a specimen to the corresponding antigen or antibody immobilized on a nitrocellulose strip either in a dipstick format or encased in a plastic cassette.

The composition of the immunochromatographic strip and the assay principle is illustrated in Fig. 27.2 for a syphilis test. During the assay process, the specimen, which can be serum, plasma, or whole blood, is applied to the sample pad well where it is absorbed by the sample pad and rapidly diffuses into the conjugate pad. If the specimen contains treponemal antibodies, it will react with the colloidal gold-treponemal antigen conjugate to form an antibody–colloidal gold complex. The complex will move along on the nitrocellulose membrane due to capillary action and react with the immobilized treponemal antigen on the Test line to form a colored band. The excess conjugate, or free conjugate if the sample does not contain treponemal antibodies, will migrate along the membrane to the Control line, where it will interact with immobilized anti-human antibody to form a colored band. Therefore, a positive sample will display two bands, one at the Test line and one at the Control line, while a negative sample will show only one band at the Control line within 10–15 min. It is important to note that the Control line is not a control for the syphilis test, but merely to show that the specimen has migrated successfully along the nitrocellulose strip. Hence when the test does not show either a test or a Control

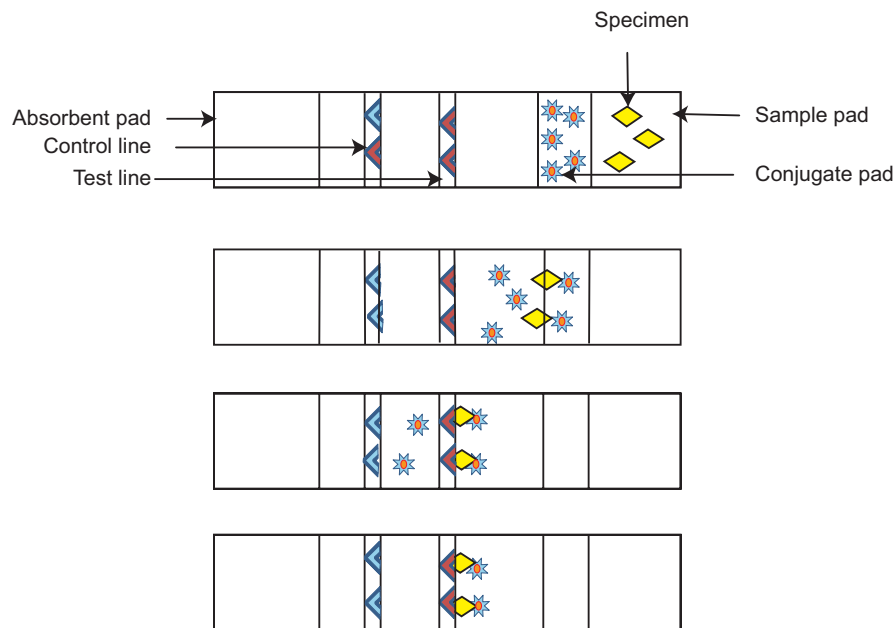
line in the reaction window, the test is invalid and needs to be repeated with the same or a different specimen.

ICTs are commercially available for the detection of bacterial STIs, human immunodeficiency virus (HIV), human papillomaviruses, and herpes simplex virus.<sup>13</sup> However, rapid tests that detect antigen require multi-step specimen processing resulting in a test with 7–14 steps which cannot be easily performed in a busy clinic.

In general, these ICTs allow increased access to diagnosis of STIs as they are stable for long periods at room temperature and are simple to perform with minimal training and no or minimal equipment. However, some ICTs are not thermostable making them less useful in developing country settings.<sup>14</sup> ICTs are inherently less sensitive than laboratory-based antigen or antibody detection tests as the antigen–antibody reaction can only take place in seconds versus over 30 min to an hour in a laboratory-based test. The trade-off between sensitivity and speed of availability of result is inevitable with this simple format. False negative tests (low sensitivity) are problematic as most clinicians accept test results over clinical findings and may fail to manage these cases appropriately. False positive tests (low specificity) lead to inaccurate diagnosis, over-treatment, and possibly stigma and blame.

### Ideal Rapid Test for STIs

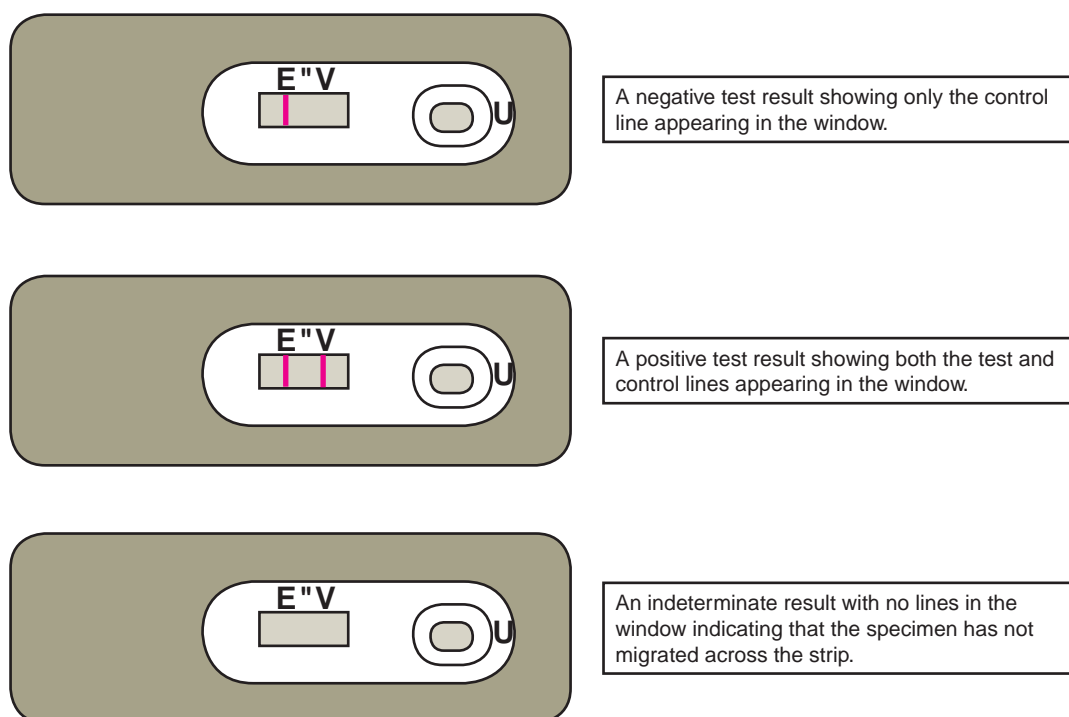
In the near future, a new generation of rapid tests that combine the ease and speed of rapid tests with the exquisite sensitivity and specificity of nucleic acid amplified tests will be available for the diagnosis of STI syndromes (Fig. 27.3).



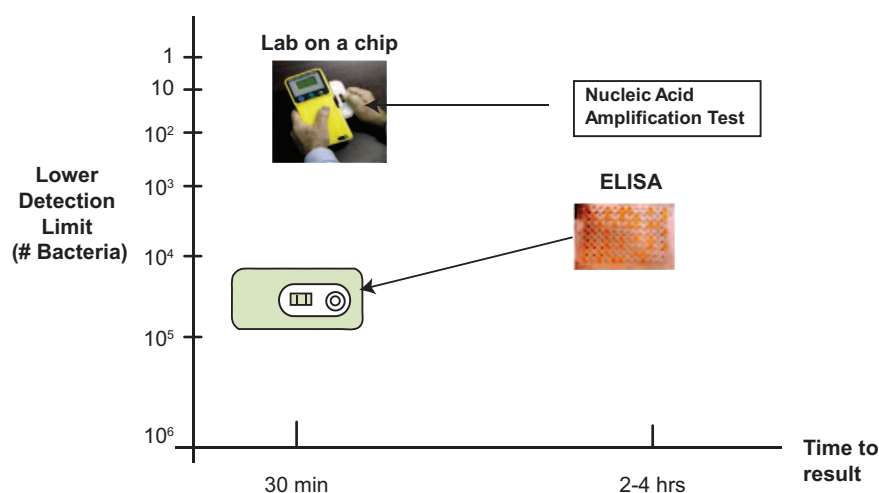
**Fig. 27.2a:** Schematic for a positive syphilis test in a lateral flow immunochromatographic format. The schematic represents four stages in the progression of a specimen containing treponemal antibodies through a lateral flow immunochromatographic strip. *Stage 1:* the treponemal antibodies represented by a yellow diamond flow from the specimen well into the sample pad. *Stage 2:* the antibodies flow through the conjugate pad and combine with colloidal gold-labeled antigen and forms a gold antigen-antibody complex. *Stage 3:* as the complex cross the Test line, it combines with the antigen immobilized on the Test line turning the Test line red. *Stage 4:* free conjugate combines with the antibody immobilized on the Control line turning it red.

If a specimen does not contain any treponemal antibodies, it would flow through the conjugate pad and the Test line without turning the line red. The free conjugate that flow through with the specimen would just turn the Control line red.

If a specimen did not migrate from the specimen well, no lines would appear in the Test line or Control line indicating an invalid assay.



**Fig. 27.2b:** Interpretation of a lateral flow assay for the detection of treponemal antibodies from a patient with syphilis.



**Fig. 27.3:** Evolution of non-culture diagnostic tests for STIs.

If rapid tests can be developed for use in health centers without traditional laboratory services, they should meet the “ASSURED” criteria developed by the WHO STD (sexually transmitted disease) Diagnostics Initiative (SDI) ([www.who.int/std\\_diagnostics](http://www.who.int/std_diagnostics))<sup>14,15</sup> (Table 27.2). The ideal test should also be a multiplex test for the detection of all the major causes of specific STI syndromes.

## Status of Current Rapid STI Tests

### SYPHILIS

Syphilis in pregnancy is a major cause of adverse pregnancy outcome in many developing countries.<sup>16–18</sup> In most countries, screening of pregnant women is a national policy but implementation rates are low because tests, such as the RPR or the VDRL slide tests, are not available in most antenatal clinics. This is because performing a non-treponemal test requires a laboratory with:

1. trained personnel;
2. refrigeration for storage of reagents;
3. electricity to run equipment: refrigerator, centrifuge to separate serum from whole blood, and a shaker to perform the serology.

Since such facilities are generally not available in rural health centers and health posts, blood or serum samples have to be transported to district or regional facilities for testing. Results

are therefore often available days or weeks after the specimens are taken.<sup>19</sup> Sometimes the specimen or the results are lost in transit. It has been estimated that approximately 30% of pregnant women are screened and treated for syphilis in sub-Saharan Africa.<sup>17</sup> A series of demonstration projects in the 1980s showed that decentralization of syphilis screening followed by immediate treatment can be effective in reducing perinatal mortality.<sup>20–23</sup> Unfortunately, decentralization has been difficult to scale up with the requirement for electricity and trained personnel.

Simple point-of-care treponemal tests, in a dipstick or cassette format, have been evaluated and shown to have sensitivities of 85–99% and specificities of 93–100% compared to laboratory-based treponemal tests.<sup>24–29</sup> These tests can be stored at room temperature and be used with whole blood obtained by finger pricks, although sensitivity can decrease by 10–20%.<sup>30</sup> More information on the performance and operational characteristics of these rapid tests can be found on the SDI website: [www.who.int/std\\_diagnostics](http://www.who.int/std_diagnostics).

A disadvantage of these rapid treponemal tests is that they cannot be used to distinguish between recent active infection and past treated infection as treponemal antibodies persist for years. However, a recent study found that treponemal tests could be more sensitive than VDRL in the detection of primary syphilis.<sup>31</sup> These tests will all be important diagnostic tools for the Global Initiative for the Elimination of Congenital Syphilis.<sup>32</sup> The advantages and disadvantages of current non-treponemal and rapid treponemal tests are summarized in Table 27.3.

In developed countries, screening and treatment of pregnant women for syphilis remain cost-effective even when the prevalence is low.<sup>33</sup> In Tanzania, where the prevalence of syphilis in pregnant women was found to be approximately 8%, it is among the most cost-effective health interventions available, at less than US\$11 per disability-adjusted life year saved.<sup>34</sup> Rapid tests cost more than current non-treponemal tests but they have been shown to be cost-effective in a number of recent studies.<sup>35–38</sup> They are particularly cost-effective when used in combination with HIV tests in Prevention of Mother to Child Transmission (PMTCT)

**Table 27.2:** The Ideal Rapid Test for STIs: ASSURED Criteria

<b>A</b>	= Affordable
<b>S</b>	= Sensitive
<b>S</b>	= Specific
<b>U</b>	= User-friendly (simple to perform in a few steps with minimal training)
<b>R</b>	= Robust and rapid (results available in less than 30 min)
<b>E</b>	= Equipment-free
<b>D</b>	= Deliverable to those who need them

**Table 27.3:** Comparison of Current Non-treponemal and Rapid Treponemal Tests

Non-treponemal tests, e.g. RPR	Rapid treponemal tests
Can be used to distinguish active from past treated infection and for test of cure	Treponemal antibodies persist for years—measure of exposure
Use serum or plasma	Use whole blood, serum, or plasma
Cannot be stored at room temperature	Test kits can be transported and stored at room temperature
Needs equipment (refrigeration of reagents, centrifuge and shaker) and trained personnel	No equipment needed
Test only takes 8 min but testing is often batched so patients are required to return for results and treatment	Results in 10–20 min and treatment given at same visit
False negative results due to prozone effect	No prozone effect

of HIV programs to prevent babies from dying of syphilis after successfully avoiding HIV.<sup>39</sup>

The greatest value of these rapid tests is in increasing the coverage of syphilis screening in rural areas of developing countries where access to laboratory services is a problem and in increasing the proportion of cases treated when return rates are low. The benefits of early detection and treatment, which prevent the serious consequences of stillbirth and congenital syphilis, outweigh the small risk of adverse drug effects associated with over-treatment.

New rapid syphilis tests that offer both non-treponemal and treponemal tests in a rapid immunochromatographic format are currently under evaluation. They allow healthcare providers to screen and confirm active syphilis infection with a single specimen at the point of care. These tools will be important for the elimination of congenital syphilis and for outreach to reduce the transmission of syphilis in high-risk populations.

## CHLAMYDIA AND GONORRHOEA

Four diagnostic companies have marketed nucleic acid amplification tests (NAATs) for the diagnosis and screening of genital chlamydial and gonococcal infections.<sup>40</sup> This has largely been driven by markets in developed countries where chlamydia screening is mandated by national STI management guidelines.<sup>41–43</sup> These tests can reliably detect 10–100 bacteria and have specificities greater than 98%.<sup>44,45</sup> The high sensitivity of NAATs makes it possible to use non-invasive specimens such as urine and self- or physician-collected vaginal swabs instead of urethral or cervical swabs. The ease of collection makes it possible to collect specimens at outreach settings or for patients to collect specimens at home and send them through the post. However, these tests are costly and are not widely available in most of the developing world where the disease burden of bacterial STIs is greatest.

More than 20 rapid tests that detect chlamydial or gonococcal antigen are commercially available worldwide. These tests are ICTs with lower limit of detection between  $10^4$  and  $10^5$  bacteria. Recent evaluations showed that although most of them have adequate specificity, they only have sensitivities of 50–70% compared to nucleic acid amplified tests for cervical swabs and 33–70% for vaginal swabs.<sup>46–48</sup> One rapid chlamydia test has been reported to have a sensitivity of more than 80% for vaginal swabs compared to urine polymerase chain reaction (PCR) in women but the test has not had any independent evaluations.<sup>49–51</sup>

Since asymptomatic individuals normally have lower bacterial load than those with symptoms, it is unclear if rapid tests of low sensitivity would be of any value for screening. A study conducted in the US showed that there might be a rapid test paradox.<sup>52</sup> In an STD clinic setting, a rapid chlamydia test with 65% sensitivity would have led to more patients being treated than an NAAT with 90% sensitivity but which requires patients to return for test results. Moreover, 3% of those infected had already developed pelvic inflammatory disease by the time they returned. Mathematical models show that the required sensitivity of a rapid test is low if there is significant STI transmission during the delay in treatment and/or few women return for treatment.<sup>53,54</sup> Hence in high-risk populations with significant possibility of transmission on a daily basis, the use of a rapid test with moderate sensitivity may be warranted in a high-prevalence setting. By giving treatment at the point-of-care and initiating partner notification, it may be possible to eliminate those with high bacterial loads from the chain of transmission within the community. This is particularly important in a high-prevalence population where patient return rates for test results and treatment are low.

## TRICHOMONIASIS

There is recent evidence that treatment of *Trichomonas vaginalis* reduces vaginal HIV shedding.<sup>55</sup> In settings where a laboratory to perform wet prep, culture, or PCR is not available, rapid tests have been developed for the detection of antigens from *Trichomonas vaginalis*. These tests have been shown to be 77–90% sensitive and 93–100% specific against culture.<sup>13,56,57</sup> However, they are more costly than the simpler tests or presumptive treatment with metronidazole.

## BACTERIAL VAGINOSIS

Bacterial vaginosis has been shown to be a factor in the acquisition of HIV and other STIs.<sup>44,45,58</sup> Women with genital discharge can be tested by pH and the amine test for the diagnosis of bacterial vaginosis if a microscope is unavailable. A number of rapid tests are available for bacterial vaginosis. They are chromogenic tests based on the detection of increased levels of microbial enzymes such as sialidases, polyamines, or trimethylamines in vaginal swab samples. They have sensitivities of 88–91% and specificity of 95% compared to the Nugent criteria.<sup>59–61</sup> One test combines a pH and the detection of proline iminopeptidase from *Gardnerella vaginalis* and has been shown



to have a sensitivity of 91% and a specificity of 62% compared to the Nugent criteria.<sup>62</sup>

### HUMAN IMMUNODEFICIENCY VIRUS

The need for rapid HIV tests to increase access to screening has driven substantial private sector investment into production of high-quality rapid HIV tests. A number of these tests have been extensively evaluated by the WHO and found to be greater than 98% sensitive and 99–100% specific compared to laboratory based tests. Details of their performance and operational characteristics are available from [www.who.int/hiv](http://www.who.int/hiv) and from the US CDC websites [www.cdc.gov/hiv/rapid\\_testing](http://www.cdc.gov/hiv/rapid_testing).

The use of these rapid tests in prenatal screening in PMTCT programs worldwide has resulted in drastic reduction in HIV transmission rates to newborns.<sup>63</sup>

The WHO recommends a three-phase approach to the use of HIV tests:

1. Evaluation of test performance in a reference laboratory using prospectively collected or archived specimens to facilitate test selection and development of testing algorithm.
2. Pilot testing algorithm at the point of service.
3. Implementation of the testing algorithm with ongoing external quality assurance and monitoring.

An assessment of this approach in 11 countries in Africa showed that in general appropriate tests were selected and the test algorithm worked well.<sup>64</sup> However, only two of 11 countries had external quality assurance programs. STD control programs should consider adopting this phased approach for the selection and use of rapid STI tests.

### HERPES SIMPLEX VIRUS TYPE 2 (HSV-2)

Rapid serologic tests for HSV-2 are commercially available.<sup>65,66</sup> They are for antibody detection and are easy to perform. Serologic tests are useful in the identification of discordant couples.

However, they are expensive and for a chronic infection such as HSV, the need for a rapid test is unclear.

### HUMAN PAPILLOMAVIRUSES (HPV)

With the introduction of two HPV vaccines, the use of HPV tests for screening has taken on a different significance.<sup>67,68</sup> A rapid test for the screening of oncogenic types in women 30 years of age or greater is commercially available. The performance of the test has not been widely evaluated but is reported to have reasonable performance against PCR.<sup>69</sup>

### Utility of Rapid STI Tests

There has been much debate whether rapid or near patient tests can improve the control of STIs.<sup>70–72</sup> The promises of rapid tests are many but so are their limitations.<sup>73</sup> Table 27.4 shows where rapid tests for STIs can make a difference.

Although the largest proportion of patients probably present to physician's offices, patients seek care at different types of clinics ranging from STI clinics, gynecology clinics, to prenatal clinics. Some present to pharmacies for treatment advice and, more recently, internet services have become more popular. Good quality rapid tests can be effectively utilized at these settings.

### PHARMACIES

Self-medication is a common practice in the developing world for many infections. This is especially true of STIs due to stigma and confidentiality issues. Many pharmacies act as surrogate clinics where the pharmacists prescribe drugs based on the self-reported symptoms of their customers. Working with pharmacists to increase their knowledge of STIs and appropriate treatment has shown good results.<sup>74,75</sup> Pharmacies can offer STI testing services or sell STI tests for home testing. Unfortunately, due to lack of regulatory oversight, many pharmacies use and sell tests with suboptimal sensitivity, giving their clients false negative results.

**Table 27.4:** Settings Where Rapid STI Tests can Make a Difference

Settings	Utility	Result
Rural or peripheral healthcare centers	Increase access to testing	<ul style="list-style-type: none"> <li>• Increased number of STIs detected and treated</li> </ul>
Health centers where syndromic management is used	<ul style="list-style-type: none"> <li>• Improve specificity of diagnosis</li> <li>• Enable partner notification and treatment</li> <li>• Reduce overuse of antibiotics</li> </ul>	<ul style="list-style-type: none"> <li>• Reduced over-treatment</li> <li>• Increased number of partners treated to prevent re-infection and onward transmission</li> </ul>
Clinics in urban centers, district and referral hospitals where laboratory services are available but STI patients need to return for results	<ul style="list-style-type: none"> <li>• Allow for immediate diagnosis and treatment</li> <li>• Prevent development of complications in the patient</li> <li>• Enable immediate partner notification and treatment</li> </ul>	<ul style="list-style-type: none"> <li>• Increased number of babies saved from still birth and congenital syphilis</li> <li>• Increased number of complications, such as cases of pelvic inflammatory disease, averted</li> <li>• Increased number of partners treated to prevent re-infection</li> </ul>
Outbreak investigation, surveillance	<ul style="list-style-type: none"> <li>• Facilitate rapid situation analysis</li> <li>• Utility in outreach and outbreak investigations</li> </ul>	<ul style="list-style-type: none"> <li>• Disease trends available for rational design of control programs</li> <li>• Increased efficacy of control and prevention programs</li> </ul>

These infected individuals may develop long-term complications and continue to transmit infection within their community.

### INTERNET SERVICES

In recent years, the internet has offered opportunities for the diagnosis of STIs.<sup>76–79</sup> There are many websites offering STI testing services or rapid test kits for home testing. These services cater to those who wish for confidentiality and to avoid stigma. Public health programs have made use of the internet to reach young people and offer excellent STI services.<sup>80–82</sup> However, most internet services and tests sold are of dubious quality as they are not subject to any regulation.<sup>83</sup>

### VENUE-BASED TESTING

Studies have shown that venue-based screening of high-risk individuals for STIs can be effective.<sup>84,85</sup> Since high-risk individuals often do not have good health seeking behavior, rapid tests offer an advantage in that testing and treatment can be offered at venues frequented by them.

## Integrated Approach for Screening of HIV and STIs

STIs have been shown to play a role in increasing the risk of HIV transmission.<sup>86</sup> Hence, opportunities for integration of STI and HIV screening at all levels of healthcare must not be missed. Individuals who test positive for one STI should immediately be offered screening for other STIs including HIV. This approach gives at risk populations a single point of access to information and services. For program managers, integrated services are more cost-effective than if the training and quality assurance of testing were provided independently.<sup>87–92</sup> In particular, rapid syphilis screening can be integrated into rapid HIV testing for PMTCT programs to avoid the tragedy of babies avoiding HIV but dying of syphilis.<sup>39</sup> Since funding for most programs are vertical, synergies between programs such as those between HIV, STIs, and reproductive health are often lost.<sup>93</sup>

## Challenges of Using Rapid Tests for STIs

If rapid tests can make a difference, and many rapid tests for STIs are currently commercially available, why are not they used more widely? The challenges faced by policy makers and control program managers are many, and they include the following.

### COSTS

Rapid tests are in most cases more expensive than laboratory tests as they are single-use tests. Laboratory tests are often batched which saves on costs and hands-on time. Decentralization of testing at different levels of the healthcare system can also require additional resources.

### LACK OF REGULATORY OVERSIGHT

In most countries in the developing world, regulatory oversight is limited or non-existent for *in vitro* diagnostics for infectious diseases, other than those used for blood banking.<sup>94,95</sup> The quality of laboratory-based tests is often better regulated through the institution of quality management systems. But this is not the case with rapid tests. As a result, many poor quality rapid tests are sold cheaply. They are bought and used without evidence of effectiveness. Companies with good quality tests will find it difficult to compete in a market that is flooded with these cheap poor quality tests.

### QUALITY CONTROL AND QUALITY ASSURANCE

With the increased access to testing and screening for STIs, it is important to ensure that the quality of the tests and the testing is maintained when tests are stored for long periods in conditions of high heat or humidity. The role of the tertiary and district level laboratories is critical in assuring the proficiency of the health workers performing rapid tests. A system of quality assurance needs to be developed and put into place as rapid tests are introduced.

## Integration into a Healthcare System

Even where there is political commitment and resources are available, there are often operational and administrative difficulties associated with the delivery of health services. In the developing world, staff shortages, lack of proper training and supervision, and frequent breakdown in the supplies of tests and medicines happen in spite of increased efforts at capacity building.<sup>96,97</sup> This means good leadership, well-trained staff, good supply chain management, quality assurance programs, and surveillance that can monitor the effectiveness of the control program or specific interventions are required.

## Future Outlook

The genomes of major bacterial STIs have been sequenced.<sup>97–99</sup> Investments in diagnostics target research will lead to the discovery of novel diagnostic targets or biomarkers, which can complement recent advances in rapid detection technologies driven and funded largely through anti-bioterrorism activities. There have therefore been more advocacy and funding opportunities for the development of new diagnostic tests to improve global health.<sup>100–103</sup> Several companies have microfluidic platforms that can test for several pathogens using a single specimen and the National Institutes of Health has funded a point-of-care test consortium to develop multiplex tests for STIs (Fig. 27.3).<sup>104,105</sup>

## Conclusions

The control of curable STIs in countries with high disease burden has been hampered by the lack of accessible STI laboratory services. Rapid tests that fulfill the ASSURED criteria have the

potential to increase the specificity of syndromic management of STIs in symptomatic patients and increase access to screening of asymptomatic infection to prevent the development of long-term complications and to interrupt the chain of transmission of STIs in the population. Increased access to testing and screening will lead to more cases of STIs being treated. Increased access to screening is critical to the success of the Global Initiative to Eliminate Congenital Syphilis and will assist countries with the attainment of their Millennium Development Goals by reducing mortality of under 5 year olds, improving reproductive health and reducing the risk of HIV transmission. Rapid tests close to fulfilling the ASSURED criteria will soon be available and can be deployed to increase access to screening in settings where testing was not previously possible or where laboratory services are inconsistent and patients return rates are low. With more political commitment and technological advances made possible by the increasing number of funders and players for test development, there is much optimism for the future for point-of-care tests for STIs that can improve patient management and disease control.

### Summary

Being frequently asymptomatic many of the sexually transmitted infections go undetected, leading transmission to the partner or the foetus with subsequent serious complications. Screening and effective treatment is critical for patient management to avoid these complications and onward transmission. Therefore, there is a great need for simple, cheap, point-of-care tests for these infections, especially in women, to increase the specificity of syndromic management and reduce over treatment of genital infections.

Historically, Gram-stained microscopy, wet-prep, pH, amine and whiff test, rapid plasma reagin (RPR-VDRL) tests do provide rapid diagnosis of most bacterial STIs; however, the tests that depend on electric supply to operate equipment, or require batching or a trained technician, remain of limited utility in the developing world. New generation rapid tests for an early and accurate detection of the infections have been introduced, most of which are point-of-care and can be used in the field without the need of maintaining the cold chain as they remain stable at room temperature. They can be performed without the use of any sophisticated equipment requiring electricity and are easily interpretable with inbuilt controls for validity of assay. Such tests are available for many sexually transmitted infections like chlamydia, gonorrhoea, trichomoniasis, bacterial vaginosis, HIV-1 and 2, HSV-2, HPV, etc. and include the slide latex agglutination assay, immunochromatography using gold conjugated detection system. Furthermore, the results are readable with naked eye. The promises of rapid tests are many, but so are their limitations.

Integration of STI and HIV screening services requires to be geared up at all levels of healthcare. This approach gives at-risk populations a single point of access to information and services. The challenges faced by policy makers and control program managers are many, and include costs, lack of regulatory oversight, and quality control and quality assurance. Besides political commitment, good leadership, well-trained staff, good supply chain management, quality assurance programs, and surveillance that can monitor the effectiveness of the control program or specific interventions are required.

With the availability of increasing number of funding agencies and players for test development there is much optimism in the future for point-of-care tests for STIs that can improve patient management and disease control.

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# section **vi**

## **VIRAL SEXUALLY TRANSMITTED INFECTIONS**

— *Raj Patel*

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# 28

## Genital Herpes Simplex Infections

Raj Patel • Sangeetha Sundaram • Bhushan Kumar

### Introduction

Herpes simplex virus (HSV) is the most common cause of infection related genital ulceration worldwide. The last four decades have seen an increase in prevalence in genital herpes infection in many population groups. The morbidity of the illness, high recurrence rates, and complications such as neonatal herpes present a challenge to both patients and physicians. More recently, the epidemiological interactions between HSV and HIV have resulted in renewed interest in the hope that stronger control of HSV may help limit the escalating HIV epidemic.

**Origin:** The word herpes (from the Greek, “to creep”) has been used in medicine for over 25 centuries. Cold sores (herpes febrilis) were described by the Roman physician Herodotus in 100 AD. John Astruc, physician to the king of France, first described genital herpes in 1736.<sup>1</sup>

### Biology

#### MORPHOLOGY

The HSV is a member of Herpes viridae family. It is a large DNA virus family that contains centrally located linear, double stranded DNA. At least eight members of the group are known to infect humans (Table 28.1).<sup>2,3</sup> Depending on the genomic and biological behavior, these human herpes viruses are divided into three subgroups (Table 28.1). The  $\alpha$ -herpes viruses replicate rapidly and infect a wide range of cells in cell culture. They are neurotropic in nature. The  $\beta$ -herpes viruses replicate slowly and enlarge infected cells. They infect a selective cell population in cell culture. The  $\gamma$ -herpes viruses also replicate relatively slowly and are lymphotropic in nature.

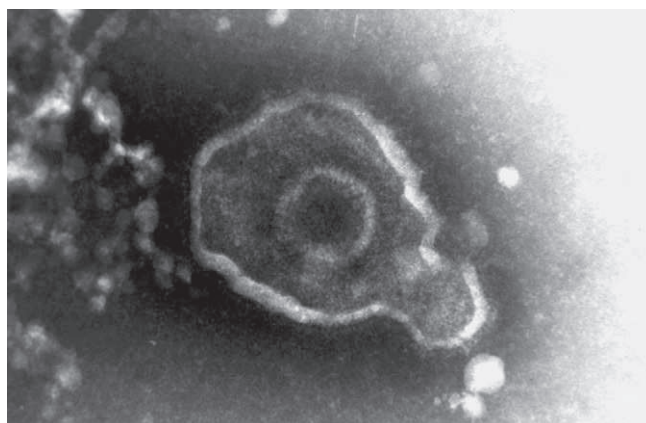
All herpes viruses are morphologically similar. They consist of four elements: (i) an electron-opaque core, (ii) an icosahedral capsid surrounding the core, (iii) an amorphous tegument containing a number of viral encoded proteins, surrounding the capsid, and (iv) an outer envelope exhibiting glycoprotein spikes on its surface (Fig. 28.1). The overall diameter of HSV is about 160 nm. The genome of HSV is a linear, double-stranded DNA

**Table 28.1:** Classification of Eight Known Human Herpes Viruses

I. Alpha herpes viruses:
(a) HSV-1
(b) HSV-2
(c) Varicella-zoster
II. Beta herpes viruses:
(a) Cytomegalovirus
(b) Human herpesvirus-6
(c) Human herpesvirus-7
III. Gamma herpes viruses:
(a) Epstein–Barr virus
(b) Kaposi sarcoma-associated herpes virus (KSHV) or Human herpes virus-8

molecule (molecular weight about  $100 \times 10^6$ ) that encodes about 80 gene products. The DNA of HSV-1 and HSV-2 are largely collinear, with reasonable, but not identical, matching of base pairs—approximately 50% of the DNA is identical.

The capsid is a protein structure, which consists of 162 capsomeres. The capsid is surrounded by a tightly adherent membrane, the tegument. The capsid and tegument are surrounded



**Fig. 28.1:** Herpes simplex virus: negative stain electron micrograph. Courtesy: CA Hart, UK.

by an envelope consisting of glycoproteins, lipids, and polyamines. The exact function of all the glycoproteins is not completely understood. The glycoproteins mediate attachment of the virus to the host cell and elicit immunological host responses to the virus. Out of the 11 glycoproteins (designated as *gB*, *gC*, *gD*, *gE*, *gG*, *gH*, *gL*, *gK*, *gL*, and *gM*), *gB* and *gC* are heparin binding glycoproteins. Some are essential for cell infection (*gB*, *gD*, *gH*, *gK*, and *gL*) while others extend the pathogenicity of the virus. Consequently, *gD*, *gB* or *gH* have become the principal targets for vaccine development. The virus attaches to the cell surface receptor (heparin sulfate) by the virion envelope, this then fuses with the cellular plasma membrane and allows the de-enveloped capsid to be transported to the nuclear pores. DNA is released into the nucleus of the cell, where a prepackaged transactivator of transcription, *VPI6*, present in the tegument, initiates the transcription of a cascade of three sets of genes. The immediate early (IE) or alpha genes initiate the replication and then activate the next set of genes, the delayed-early or beta genes. The beta genes produce enzymes necessary for viral replication, such as HSV thymidine kinase and DNA polymerase. The onset of expression of beta genes coincides with both the decline in the rate of expression of alpha genes and an irreversible shut off of the host cellular macromolecular protein synthesis (causing cell death). Gamma genes are the last to be expressed and code for structural proteins.

Assembly of the herpes virus nucleocapsids begins in the nucleus. The nucleocapsids then acquire the envelope as they bud through the inner lamella of the nuclear membrane. The enveloped particles are then transported through the cytoplasm to the plasma membrane by membrane-bound vesicles and the Golgi apparatus. The release of progeny virions occurs at the plasma membrane. The replicative efficiency of HSV is poor, as the ratio of infectious to incomplete virions is low. Productive herpes virus infection to the host cell is fatal. It also induces cell–cell fusion (polykaryocytosis), which may function as an alternative method for viral spread from one cell to another and could facilitate evasion of host immune responses.

## LATENCY

Latency is a common property of all the herpes viruses, which enables them to persist for the entire lifetime of their natural host. During latency, the viral genome is maintained in the host cell nucleus with expression of only a limited subset of viral genes. The only site of latency for HSV is the sensory ganglia of nerves innervating the initial site of infection or those subsequently inoculated. Following infection, cell-mediated immunity clears actively replicating virus from the body. Some virus, which is not cleared, remains in a virtually inactive state within neuronal tissue. This latent virus is maintained for life as extrachromosomal genetic elements (episomes) and may reactivate at any time. During latency there is a low level of DNA transcription and small amounts of viral RNA can be detected in the neuronal tissue—all of which appear to be derived from a single area

of the genome. These latency associated transcripts (LATs) are unique to HSV type and are not required for the maintenance of latency. They do have an important role in reactivation and in this they appear to act as “environmental thermometers.” Anatomical site-specific patterns of recurrence are mediated by the LATs region of the genome.

## HOST IMMUNE RESPONSE

Both innate and adaptive cell-mediated immunity are critical for limiting the spread of HSV infection and controlling viral replication.<sup>4–6</sup> Cell-mediated immunity against HSV infected cells involves NK cells, activated T cells, and macrophages. Cytokines released by lymphocytes may have direct antiviral activity or may regulate other components of the host immune response. Cytotoxic T-lymphocytes are important in the resolution of cutaneous lesions. The cellular immune response is the main factor in determining both the severity and the rate of recurrence of HSV. Both CD8+ and CD4+ lymphocyte subsets have a role in mediating protection against HSV.<sup>7</sup> Neutralizing and antibody-dependent cellular cytotoxic antibodies appear 2–6 weeks after infection and persist lifelong. Humoral immunity does not prevent recurrences or exogenous reinfections, although the thresholds for infection are raised. Antibodies acquired transplacentally are not totally protective against vertical or neonatal HSV infection. HSV recurrence is not a consequence of low antibody titer; high titers of antibodies have been shown in some studies to correlate with both a high frequency and severity of recurrent disease in adults.<sup>8,9</sup>

## REACTIVATION

The reactivation process, in many instances, has been found to be prostaglandin associated. Trauma, such as UV radiation, tape stripping of the skin, and application of retinoic acid cause reactivation in experimental models. These stimuli are associated with a local elevation of E and F class prostaglandins. Prostaglandins are rapidly synthesized in plasma membranes in response to tissue injury and are released into the extracellular space to act on target tissues. PGE<sub>2</sub> elevates cyclic AMP in target cells. Recurrences may be spontaneous or precipitated by physical or emotional stress, fever, UV light, cold, heat, food allergy, fatigue, concurrent infection, tissue damage or immunosuppression. A putative mechanism for this may be that these factors release first-order messengers, like prostaglandins, locally, or epinephrine or other “stress” hormones, systemically. These in turn elevate levels of intracellular second messengers like cAMP, which reactivate the HSV.<sup>10</sup>

## HSV AND CARCINOGENESIS

HSV DNA has been shown to induce point mutations, gene rearrangements, and gene amplifications in cells. It can also switch on exogenous DNA in cells, such as those from latent type C retrovirus and HIV, and it may switch on genes that are

not normally expressed. Despite its transforming ability, HSV alone will not induce cancer in intact animals. In one *in vitro* study, insertion of the transforming region of HSV-1 into human oral keratinocytes did not induce a malignant phenotype. In conclusion, HSV is not a primary carcinogen but can facilitate a carcinogenic process.

## Epidemiology

HSV infections are endemic throughout the world. Changing behavioral patterns particularly since the emergence of the HIV epidemic have resulted in significant alterations in the patterns of STI epidemics. Much is known about the extent of HSV infection in the developed world and Africa but there is a relative paucity of population-based studies conducted in Asian countries. In Asian countries, increased condom use and reduction in sexual contact with sex workers are responsible for reduced prevalence of many bacterial STDs.<sup>11</sup> This has resulted in a shift from syphilis and chancroid to genital herpes as the dominant cause of genital ulcer disease. Reported HSV-2 prevalence in India varies between 1.0% and 18.9% from general population-based surveys,<sup>12–16</sup> between 9.7% and 83% from STD clinics,<sup>17–19</sup> and between 2.0% and 79% from high risk group surveys.<sup>20–23</sup> A recent survey conducted in three major towns in India showed a 10.1% prevalence of HSV-2 and that prevalence increased significantly with increasing age.<sup>24</sup>

Genital herpes is the most common cause of genital ulceration in the developed world. In UK, more than 30,000 cases (2009), and in USA, more than 50,000 new cases of genital herpes are estimated to occur every year. Findings of the CDC's National Health and Nutrition Examination Survey (NHANES) estimate HSV-2 prevalence in the USA in 2005–2008 at 16.2%. This

represents only a slight decline from the last national estimate of 17% (1999–2004) indicating that HSV-2 seroprevalence rates are relatively stable. The survey also showed that HSV-2 prevalence was nearly twice as high among women (20.9%) than men (11.5%), and was more than three times higher among blacks (39.2%) than whites (12.3%). Worldwide, HSV-2 prevalence appears lower in Europe, including UK (9.7%), Eastern Europe (6–25%),<sup>25,26</sup> and Australia (16% in women, 8% in men).<sup>27,28</sup>

There is a paucity of population-based studies from developing countries. A seroepidemiological study conducted in selected populations in Brazil, Estonia, India, Morocco, and Sri Lanka showed that Brazil had the highest age-specific rates of infection for both men and women, followed by Sri Lanka for men and Estonia for women, the lowest rates being found in Estonia for men and India for women.<sup>29</sup> In all countries, HSV-2 seroprevalence increased significantly with age and adult females had higher rates of infection than adult males by age of infection. Among pregnant women prevalence has been estimated at 27% in Saudi Arabia<sup>30</sup> and 30% in the south pacific region.<sup>31</sup> Population-based studies in Africa indicate very high level of infection, for example, in South Africa, HSV-2 infection rates reach 80% in women and 40% in men by age 24.<sup>32</sup> In Latin America, infection rates range from 20% in women in Peru to 43% in female blood donors in Brazil to over 60% among men in STD clinics.<sup>33</sup> Figure 28.2 shows seroprevalence of HSV-2 in different countries. Seroprevalence of HSV-2 in selected populations is shown in Table 28.2.<sup>34–39</sup>

About 40% of newly acquired HSV-2 infections and about two-thirds of new HSV-1 infections are symptomatic. Among sexually active adults, new genital HSV infections are as common as new oropharyngeal HSV infections.<sup>40</sup> More than 85% of those identified only by HSV-2 serology will still shed virus from the genital tract over

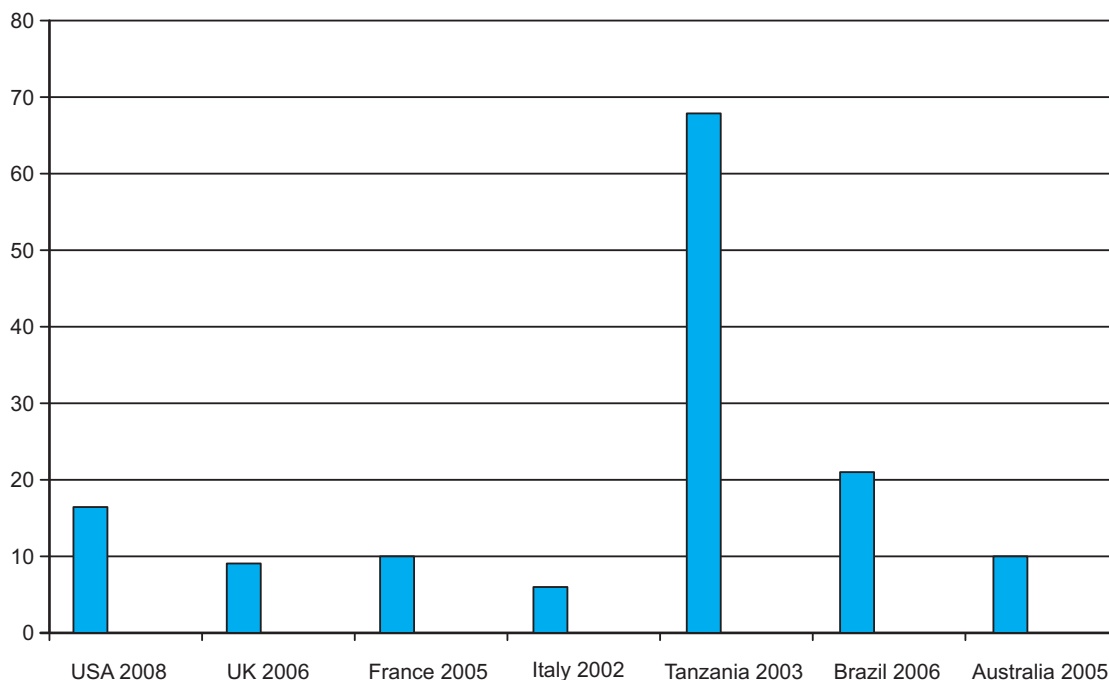


Fig. 28.2: Seroprevalence of HSV-2 in population-based studies.



**Table 28.2:** Seroprevalence in Selected Populations (Worldwide)<sup>34–39</sup>

Patient/population group	HSV-2 seropositivity (%)
STD-clinic attendees (males)	8–65
(females)	22–55
STD-clinic attendees (both males and females)	31–83
Female prostitutes	75–96
Antenatal clinic attendees	36–53
University students	2–4
Adolescents	8–14
Infertile women	4

short periods of time<sup>19</sup>—it is generally accepted that everyone with HSV infection will shed virus in the long run. Many who acquire infection subclinically, later develop clinical recurrences.<sup>19</sup> Most cases of genital herpes are caused by HSV-2, however an increase in the incidence of genital herpes caused by HSV-1 has been reported from Europe, North America, and Australia.<sup>41–44</sup> Laboratory-based studies have identified a predominance of HSV-1 in genital lesions particularly in young people, women and men who have sex with men.<sup>45,46</sup> Many explanations have been given for more frequent occurrence of HSV-1 genital herpes. Firstly, HSV infections during childhood seem to have decreased.<sup>47,48</sup> Presence of antibody to HSV-1 correlates inversely with socio-economic status and is lowest in the developed world. Surveys in western populations have shown that 80–100% of middle-aged adults of lower socioeconomic status had been exposed to HSV-1 as compared with 30–50% of adults of higher socio-economic groups. The lower prevalence of HSV-1 immunity in children has meant that many more young adults are susceptible to HSV-1 when they become sexually active.<sup>48</sup> Secondly, greater frequency of orogenital sex as a result of “safer-sex” programs could add to this changing trend. A third possibility could be a change in viral pathogenicity.<sup>47</sup> The average annual seroincidence rates are 1.8% for HSV-1 and 1.4% for HSV-2.<sup>24,49</sup>

Pre-existing antibodies to HSV 1 often predisposes to asymptomatic genital acquisition of HSV 2 or clinically milder HSV2. Persons with prior HSV-1 infection are less likely to have systemic symptoms and have a shorter duration of symptoms and signs. Prior HSV-1 infection, however, does not alter the subsequent recurrence rate of genital HSV-2 disease.

HSV-2 seroprevalence is affected by age (antibodies are not seen until puberty), female gender, ethnicity, lifetime number of sexual partners and history of other sexually transmitted infections (e.g., gonorrhea, syphilis, and genital warts). As such, presence of HSV-2 antibody serves as a serological marker for sexual behavior in the general population and high-risk groups.<sup>50</sup>

## Transmission

The transmission of HSV-2 is more frequent from men to women than from women to men. Couple studies have shown transmission rates between 3% and 12% per year.<sup>51–54</sup> Men are more likely

to acquire HSV-2 asymptotically than women. In one study, the risk of acquisition of HSV-2 was found to be 32% in HSV seronegative women, while only 6% or less in men. The higher rates of asymptomatic infection in men may be a factor in the higher rate of male to female (as compared with female to male) transmission of HSV-2. A recently published report indicates that bacterial vaginosis (BV) appears to enhance the risk of acquisition of genital herpes simplex infection.<sup>55</sup> An analysis of results showed those who initially had BV were nearly twice more likely to have acquired the HSV-2 infection than those without BV.<sup>55</sup>

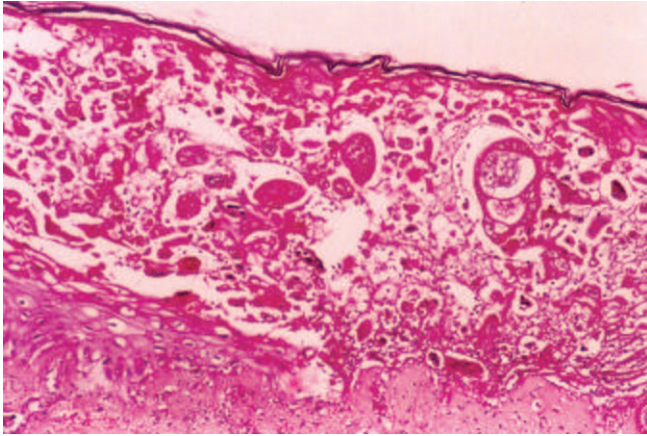
Asymptomatic viral shedding is the primary mode of herpes virus transmission. In 50–90% of instances of transmission, the infected partner is unaware of herpes infection. Asymptomatic shedding occurs most frequently in the first year after the primary episode. In a recent study of 30 HIV negative, HSV-2 seropositive homosexual men, it was found that 53.3% of these men shed HSV-2 on 3.1% of the days.<sup>56</sup> The risk of transmission is greater with HSV-2 as compared with HSV-1 isolates, from males to females and in non-users of barrier methods of contraception.<sup>35</sup> In longitudinal couple studies the median time of the relationship before transmission occurred was 3 months and the median number of sexual encounters was 24, suggesting that HSV is relatively easy to transmit. Source partner's awareness of the infection and disclosure to the sexual partner is associated with a 50% decrease in the risk of HSV-2 transmission.<sup>57</sup> Longitudinal transmission studies demonstrate that transmission rates per act of sexual intercourse decline as a relationship matures. It is unclear why this should be but may simply be a frailty effect with those relationships most susceptible to transmission through high shedding in one partner or particular risk factors for acquisition in the other managing to transmit early leaving a population who are more resistant to transmission with time.

In most cases of neonatal HSV infections, the mothers have no history of genital disease.<sup>58</sup> Mothers who acquire primary sub-clinical infection near term and who are asymptotically shedding the virus are at high risk of transmitting the HSV virus to the neonate.<sup>16</sup> In the presence of a history of recurrent lesions in the mother, the vertical transmission rate is much lower (<5%).<sup>16</sup> The passive transfer of maternal antibodies protects to some extent against severe neonatal herpes and raises the threshold for infection.

## Pathology

The histological features of herpes simplex type 1 and type 2, varicella and herpes zoster are similar. They represent a combination of virally mediated cellular death and the associated cellular response. The earliest epidermal cell changes appear in the nuclei, in the form of peripheral clumping of chromatin and a homogenous ground glass appearance combined with ballooning of the nucleus.<sup>59</sup> The earliest cytoplasmic alteration is vacuolization. The cells lose intact plasma membranes and form multi-nucleated giant cells. Initially, these changes appear in the basal layer, but later involve the full thickness of the epidermis. Two types of degenerative changes appear leading to intraepidermal vesicle formation—ballooning degeneration and reticular degeneration. In ballooning degeneration, the affected cells swell and lose their attachment to adjacent cells resulting





**Fig. 28.3:** Histology of genital herpes showing ballooning degeneration, spongiosis, and acantholysis (H&E, × 550). *Courtesy: Uma Nahar and BD Radotra, Chandigarh, India.*

in secondary acantholysis. This is characteristic of viral infections (Fig. 28.3). The acantholytic or Tzanck cells have homogenous and intensely eosinophilic cytoplasm. In reticular degeneration, there is progressive hydropic swelling of epidermal cells, which become large and clear. These eventually rupture leading to vesicle formation. Such “spongiotic” changes are not characteristic of a viral bulla and are also seen in other diseases like allergic contact dermatitis. Eosinophilic intranuclear inclusion bodies are seen in the swollen cells. Neutrophils and lymphocytes are predominant in the infiltrate.

## Cytodiagnosis

The Tzanck smear is taken from a recent lesion. The intact roof of the vesicle is opened along one side, then folded back and the bottom gently scraped. The material is smeared onto a glass slide, allowed to air dry, and stained with May–Grunwald–Giemsa stain

for 20–25 minutes.<sup>60</sup> The cytologic picture cannot differentiate between HSV-1, HSV-2, and varicella, and is frequently unhelpful even though virus can be isolated by other more reliable methods. In all of these conditions multi-nucleated giant keratinocytes are found (see Chapter 26, “Laboratory Diagnosis of Sexually Transmitted Infections”). The cells look as if they have been inflated (ballooning degeneration). The nucleus shows some blurring of the chromatin pattern and loss of staining. Intranuclear inclusion bodies surrounded by a clear halo are characteristic of herpetic infection, but are not always easy to find on smear.

## Clinical Manifestations

HSV causes a wide variety of disorders in adults and neonates (Table 28.3).<sup>61</sup> In addition to physical illness, it may also cause psychological and psychosocial problems.<sup>61</sup> To understand the clinical manifestations of genital herpes, it is important to differentiate between the first clinical episode and recurrent episodes, because the course and natural history of these entities are different (Fig. 28.4).

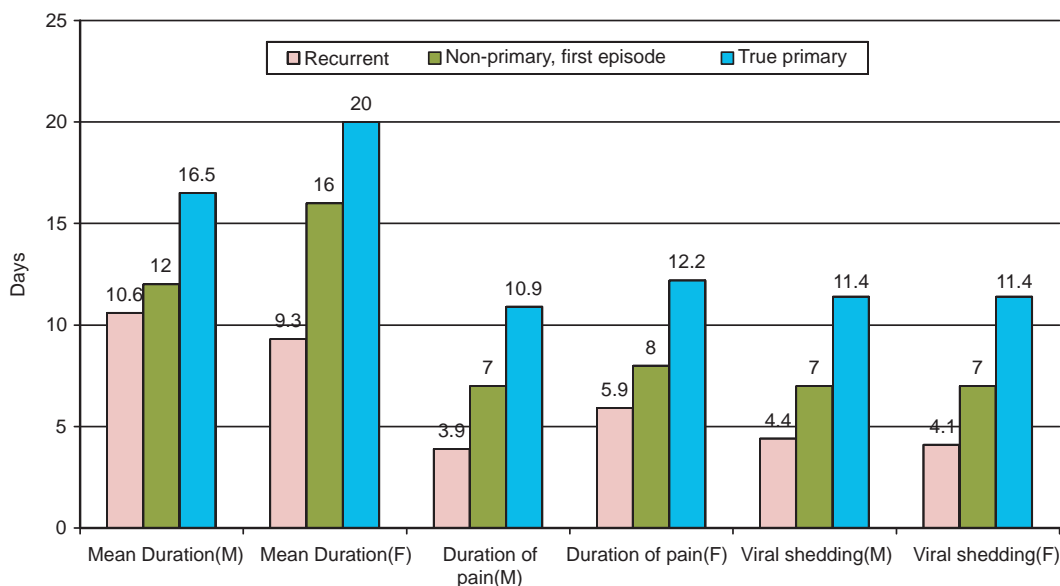
**Table 28.3:** HSV Infections in Humans<sup>17</sup>

### In immunocompetent hosts:

- Orolabial herpes
- Anogenital herpes
- Ophthalmic herpes
- Aseptic meningitis, myelitis
- Other sites (e.g., herpetic whitlows affecting fingers)

### In immunocompromised hosts:

- Progressive/persistent (chronic) mucocutaneous ulcerations
- Disseminated infection
- Encephalitis
- Pneumonitis
- Colitis, esophagitis
- Hepatitis



**Fig. 28.4:** Mean duration of ulcers, pain, and viral shedding in men and women in true primary, non-primary first episode and recurrent genital herpes (M–males, F–females).

**Table 28.4:** Classification of Symptomatic Genital Herpes Depending upon Paired Serologic Results and Viral Isolation

HSV type isolated	Acute phase serology		Convalescent phase serology		Classification
	HSV-1	HSV-2	HSV-1	HSV-2	
HSV-1	–	–	+	–	Primary HSV-1
HSV-2	–	–	–	+	Primary HSV-2
HSV-1	–	+	+	+	Primary HSV-1 in previously HSV-2 infected Individuals (uncommon)
HSV-2	+	–	+	+	Primary HSV-2 in previous -1 infected individuals
HSV-1	+	– or +	+	– or +	Recurrent HSV-1
HSV-2	– or +	+	– or +	+	Recurrent HSV-2

The severity of clinical manifestations and the recurrence rate of genital herpes are influenced by both viral and host factors. The first clinical episode can further be sub-divided into primary infection, occurring in a person without prior HSV-1 or HSV-2 antibody, or non-primary infection, occurring in a person with prior HSV-1/HSV-2 antibody (Table 28.4). The majority of HSV infections (both HSV-1 and HSV-2) are subclinical.

### PRIMARY GENITAL HERPES

Primary genital herpes is classically characterized by prolonged systemic and local symptoms. Pain, dysuria, urethral or vaginal discharge, genital and sacral paresthesia, and tender inguinal lymphadenopathy are the predominant local symptoms.<sup>62</sup> Lesions appear 3–14 days after exposure. Systemic symptoms appear early in the course of the disease, they begin after a mean incubation period of 6–8 days, peak within 4 days of onset of lesions and gradually abate over the subsequent 3–4 days. About 40% of men and 70% of women experience constitutional symptoms during primary disease. Headache, fever, myalgias, lethargy, backache, and photophobia are the most frequent complaints.

Local symptoms of itching, erythema, and pain usually precede visible lesions by 1–2 days. The first lesions typically are small, grouped, painful vesicles or pustules on an erythematous base, which break and form ulcers in 2–4 days. Initial lesions may involve an extensive area (Figs. 28.5 and 28.6) and individual lesions may coalesce to form large ulcers. Atypical features including the development of deep necrotic ulcers may also occur. New groups of lesions may appear during the second week. In the third week, crusts appear over lesions and the process of re-epithelialization begins. Crusting does not occur on mucosal surfaces and scarring from lesions is uncommon. Tender inguinal lymphadenopathy appears during the second or third week and may persist despite lesions healing. Involved inguinal and femoral lymph nodes are tender to palpation, firm, and non-fluctuant.

Isolated HSV cervicitis may be a sole manifestation of the first episode in about 8% of women,<sup>63</sup> however 88% of women with



**Fig. 28.5:** Widespread lesions on shaft of the penis of true primary genital herpes.



**Fig. 28.6:** Extensive vulval lesions of primary genital herpes.



primary genital HSV-2 infection have HSV-2 cervicitis.<sup>64</sup> HSV urethritis may occur as the only symptomatic manifestation in less than 5% of both men and women.<sup>65</sup> Urethral discharge and dysuria are present in about one third of men. The discharge is clear and mucoid. The severity of dysuria is out of proportion to the amount of discharge.<sup>66</sup> HSV viral pharyngitis (sore throat) can occur and HSV can be isolated from the throat in 11% of all the patients with HSV-2 genital disease.<sup>67</sup> The mean time from onset of lesions to complete healing is longer in women (about 20 days) than in men (16.5 days). The mean duration of viral shedding, as defined from the onset of lesions to the last positive culture is 12 days.<sup>67</sup>

### FIRST EPISODE NON-PRIMARY GENITAL HERPES

About 50% of patients, presenting with their first clinical episode of genital herpes, have pre-existing antibodies to either HSV-1 or HSV-2.<sup>15</sup> Most patients with first episode genital ulceration due to HSV-2 have serological evidence of prior HSV-1 infection<sup>68</sup>; acquisition of HSV-1 in persons with prior HSV-2 infection is rare. Neutralizing antibodies to HSV inactivate extracellular virus and interrupt the spread of HSV infection. The cellular response to HSV antigen also appears earlier in persons with non-primary genital herpes than in post-primary first episode. Those with non-primary first episode have lower frequencies of systemic symptoms, shorter durations of pain, fewer lesions, and shorter healing times compared with true primary infections. Constitutional symptoms are present in only 16% of patients, in contrast to 70% of the patients with true primary disease. Lesions are not widely distributed, they may be unilateral, and the mean surface area is only one-third of that in true primary disease. The mean number of days with pain, healing time, and viral shedding is about 4 days less than in true primary disease.<sup>67,69</sup>

### FIRST EPISODE IN HSV-2

#### Seropositive Patients

Diamond et al.<sup>70</sup> reported that 41 (8%) out of 498 patients, clinically judged to have first-episode HSV-2 of genital herpes, had serologic evidence of previously acquired HSV-2 infection. Bernstein et al.<sup>71</sup> have also reported that 75% of the persons thought to have first-episode non-primary infection (first episode HSV-2 infection in a person with serologic evidence of prior HSV-1 infection) had pre-existing HSV-2 antibodies. These studies have important implications upon patient management particularly around counseling and education around timing of actual infection and possible sources of HSV. The knowledge that their current sex partner may not be the source of their infection and that persons who transmit HSV are usually not aware that they have genital herpes may help in stabilizing a relationship weakened by the unexpected development of genital herpes in one partner.<sup>72</sup> When available, type-specific serologic testing and virus culture and typing during the first clinical episode can accurately determine, whether acquisition of infection was recent or remote.<sup>72</sup>

### RECURRENT GENITAL HERPES

Genital herpes caused by HSV-2 is recurrent in at least 90% of infected patients and 88% have at least one recurrence within 12 months of their initial episode (Fig. 28.7).<sup>67</sup> The mean rate of recurrence in HSV-2 genital infection is 0.3–0.4/month.<sup>67</sup> In genital herpes caused by HSV-1, 55% patients report recurrent episodes with a mean recurrence rate of 0.09/month.<sup>67</sup> Men have more recurrences than women, also, patients who had a prolonged primary infection (more than 34 days) had more frequent recurrences than those who healed faster. The change in recurrence rate over time is not clear. Some studies reported a reduction in recurrence rate after 18 months<sup>73</sup>; others found no consistent change in recurrence rate even after 5 years.

Recent long-term cohort studies, however, indicate that the frequency of symptomatic episodes gradually decreases by median of one recurrence per year.<sup>66</sup> Reactivation, both symptomatic and subclinical, is less frequent with genital HSV-1 infection when compared to genital HSV-2 infection. Recurrences can be triggered by emotional stress, sunlight, concurrent infections, and menstruation.

### Atypical Manifestations

It is not uncommon to see patients with genital herpes presenting with atypical features (Table 28.5). Genital herpes may be misdiagnosed as recurrent vaginitis, urinary tract infections or *Candida* infection in women and as folliculitis, condom allergy,



Fig. 28.7: Recurrent lesions of genital herpes.

Table 28.5: Some Atypical Presentations of Genital Herpes

- Vaginal discharge (unrelated to candidiasis)
- Genitourinary pain
- Non-specific vulvar erythema
- Prostatitis and lower back pain
- Itching, burning, soreness or pain over genitalia (without apparent lesions)
- Unexplained systemic symptoms, like fever, malaise, and myalgia
- Vulvar, penile or perianal fissures
- Folliculitis

and other dermatoses in men.<sup>74</sup> It is important to remember that people having circulating antibodies against HSV-1, who are newly infected with HSV-2, are less likely to present with classical signs and symptoms. As recent epidemiological data indicate HSV as the most common cause of genital ulcer disease, clinicians should evaluate all genital lesions, regardless of appearance for herpes.

### Psychological Factors in Recurrences

Stress is invoked as an important factor for precipitation of recurrences. Evidence suggests that patients with high levels of recurrences are more likely to blame stress than those with less frequent recurrences. However, the role of stress as precipitating factor has not been conclusively proven and there is a possibility that there might be a mood/cognitive elements to the prodrome in recurrent herpes, which may be misinterpreted as stress.<sup>75,76</sup> A recent prospective study has shown that single stressful events are not related to recurrences. While long-term stress (lasting more than 7 days) is related to recurrences. It has also been shown that more intense long-term stress is more closely related to an increased chance of recurrences.<sup>77,78</sup>

### Prodrome in Recurrent Genital Herpes

Many individuals with genital HSV infection are able to predict a recurrence of genital HSV through warning prodromal sensations. In one study, 59% of the subjects could reliably predict the onset of an episode on at least 75% of occasions by the presence of prodromal symptoms.<sup>79</sup> Localized prodromal symptoms usually appear in the form of mild tingling sensations up to 48 hours prior to any eruption.<sup>66</sup> Sometimes, shooting pains in the buttocks, legs or hips may appear 1–5 days prior to the episode. Rarely sacral neuralgia may occur.<sup>66</sup> The risk of viral shedding is high during prodromal symptoms, even in the absence of lesions. False prodromes (prodromal symptoms that do not progress to visible genital signs) do occur and are more frequent in those with more frequent recurrent disease.

### Factors Influencing Recurrence Rates

Animal studies shown that these might include inoculum size, severity of acquisition infection, herpes virus types (more genital recurrences with HSV-2 infection) and early antiviral treatment of a first episode. However, clinically only the viral type, primary or non-primary nature and extreme length of an acquisition episode have been associated with subsequent disease severity.

### Clinical Features of Recurrent Genital Herpes

Recurrent genital herpes is the mildest form of the disease. Only a limited number of vesicles, usually 3–5 in number, appear on the shaft of the penis/glans/prepuce of male patients. Although symptoms of recurrent genital herpes are more severe in women, objective clinical signs are relatively similar in both sexes. The disease is usually unilateral. Constitutional symptoms are seen

only in 5% of men and 12% of women.<sup>67</sup> The cervix is involved in 12% of episodes. The urethra is involved in 4% of the patients and 4% will develop extragenital lesions.<sup>80</sup> Painful genital ulcers occur more frequently in women than in men (88% vs. 67%),<sup>67</sup> which also persist for a longer duration (5.9 days vs. 3.9 days). There is considerable variability in the severity and duration of disease both among patients and in a patient between episodes. Only one-tenth the area involved in primary genital herpes is affected in recurrent disease. Viral shedding peaks by 48 hours from the onset of lesions and lasts for about 4 days. The mean time from onset to crusting is about 5 days in both men and women.<sup>66</sup> Complete re-epithelialization occurs in about 6–10 days.<sup>66</sup> Sometimes the episode can be abortive, characterized by itching, redness and edema but no vesicles, ulcers or crusts.

### GENITAL HERPES IN IMMUNOCOMPROMISED HOSTS

All the manifestations of HSV infections seen in the immunocompetent host can also be seen in immunocompromised patients, but they are usually more severe, extensive, difficult to treat and more frequent (Fig. 28.8).<sup>81</sup> In advanced immunodeficiency dissemination of HSV may also be seen. Recurrent and persistent ulcerative HSV lesions are among the most common infections among patients with AIDS.



**Fig. 28.8:** Chronic, large ulcers of genital herpes in a HIV seropositive immunosuppressed patient.



Atypical presentation of HSV infection can occur in patients with HIV infection,<sup>82–84</sup> hematologic malignancies,<sup>85</sup> organ transplant recipients, and congenital immunodeficiencies.<sup>86,87</sup> Mucocutaneous HSV infections in the immunocompromised host may be associated with prolonged local symptoms, systemic complaints, and a prolonged viral shedding beyond 30 days. Atypical infections may present with the following features:

- **Hyperkeratotic, verrucous (wart) lesions<sup>82,84</sup>:** In patients with advanced HIV infection, HSV may present as verrucous or warty lesions. Sometimes, the genital lesions of HSV acquire a large size, become papillomatous with a verrucous surface and may closely mimic condyloma acuminata or verrucous carcinoma. The histopathology, however, is characteristic and shows acantholytic and giant cells.
- **Vegetating plaques<sup>86</sup>:** Expanding, confluent, vegetating plaques with ulceration and a yellow exudate have been reported due to HSV genital infection.
- **Chronic, persistent ulceration:** Extremely painful, persistent, large, necrotizing ulcerated areas involving the whole perineum in females or the prepuce, glans, shaft of the penis, and pubic region in male.
- **Generalized papular eruptions:** Generalized exanthematous eruption can occur rarely as a result of dissemination in an immunocompromised host. This should be considered a medical emergency.

## Complications of Genital Herpes

Complications of genital herpes are nearly always associated with primary disease and are usually more severe in women than in men. Psychological, central nervous system (CNS) complications and secondary microbial infections are the commonest (Table 28.6).

### ASEPTIC MENINGITIS

HSV has been isolated from CSF of 0.5–3% of patients presenting with aseptic meningitis. HSV-2 is more commonly isolated than HSV-1.<sup>88</sup>

Genital lesions are present in only about one-third of the patients with HSV-2 meningitis. HSV can also be isolated from CSF of otherwise normal individuals. About 36% of women and 13% of men with primary HSV-2 genital infection develop this complication.<sup>67</sup> Genital lesions precede meningitis by about 1 week (range 3–12 days).<sup>89</sup> The symptoms of aseptic meningitis

include headache, rigid neck, vomiting, photophobia, malaise, and fever. The symptoms usually peak within 2–4 days and then gradually subside over 2–3 days. The CSF demonstrates a lymphocytic pleocytosis ranging from 5 to more than 1000/mm<sup>3</sup> (median 300–400/mm<sup>3</sup>) with a raised glucose (more than 50% of the blood glucose). HSV-2 meningitis resolves fully in the majority of individuals without any neurological damage.<sup>67</sup> Patients may occasionally present with aseptic meningitis as the sole presenting sign of new HSV-2 acquisition; in these cases, detecting the virus in the CSF and the lack of serum antibodies to the autologous virus type is diagnostic.

In primary genital herpes associated meningitis, transient neurological complications, such as urinary retention, dysesthesia, paraesthesias, neuralgias, motor weakness, paraparesis, concentration difficulties, periodic headache, and impaired hearing have been reported.<sup>89</sup> About 20–30% patients may have recurrent meningitis (benign recurrent lymphocytic meningitis or Mollaret meningitis).<sup>89</sup> There are no controlled trials for the use of intravenous (IV) acyclovir in the treatment of established HSV meningitis; however, it is recommended that symptomatic hospitalized patients be treated with IV Acyclovir 5 mg/kg 8 hourly and switched to oral antivirals preferably valacyclovir once symptoms have resolved.

### RADICULOMYELOPATHY

This is characterized by symptoms of sensory and autonomic nervous system dysfunction; numbness, paresthesia, neuralgic pain of the buttock, perineum or lower limbs, urinary retention, constipation and/or impotence. Clinical signs include sacral anesthesia, hyperesthesia, reduced perineal, and bulbocavernous reflexes, reduced rectal sphincter tone and bladder distension. Pleocytosis, elevated protein, and lower glucose may occur in the CSF.<sup>88</sup> Symptoms gradually resolve over days to weeks. Sometimes, residual urinary dysfunction, hyperesthesia of the lower extremities and weakness may persist for months.<sup>88</sup> The condition is particularly common in homosexuals with HSV proctitis.<sup>90</sup> Heterosexual women with primary genital herpes are the next most common subgroup prone to this complication.<sup>66</sup> Urinary retention in herpes genitalis predominantly occurs in females about 4 days after the appearance of lesions<sup>88</sup> and recovers in 3 days to 3 weeks. It is not clear whether demyelination is due directly to viral inflammation or indirectly to post-infectious inflammation. In reactivation disease, neuralgic pain and/or dysesthesia can occur in the form of prodromal symptoms at the site of the oncoming lesions or sometimes at a distal site within the distribution of the same ganglion. In abortive episodes, patients may experience only prodromes with no subsequent lesions. Rarely, the typical episodic prodromal pain of recurrent HSV infection acquires a chronic persistent course resembling post-herpetic neuralgia of herpes zoster, which may be associated with neurological deficit.<sup>88</sup>

### HSV ENCEPHALITIS

HSV infection is the most common cause of the sporadic fatal encephalitis.<sup>91</sup> The manifestations depend on the areas of the brain

**Table 28.6:** Major Sequelae of Genital Herpes

- |       |  |
|-------|--|
| (i)   | Psychological morbidity associated with recurrences                                  |
| (ii)  | Psychological morbidity related to fear of transmission to partner or fetus/newborn  |
| (iii) | Systemic complications such as aseptic meningitis or urinary retention               |
| (iv)  | Disseminated infection, mainly in immunocompromised host or in pregnancy (very rare) |
| (v)   | Transmission to the newborn (potentially fatal, fortunately rare)                    |
| (vi)  | Increased risk of acquiring/transmitting HIV infections                              |

affected. The clinical features include fever, altered consciousness, bizarre behavior, disordered mentation, and localized neurological findings. The mortality among untreated patients is up to 76% and only 2.5% of those who survive regain normal neurologic function.<sup>91</sup> A number of genetic predispositions to the development of HSV encephalitis have been described.

### DISSEMINATED INFECTION

This is seen in immunocompromised hosts such as post-organ transplantation, malignancy, malnutrition, alcoholism, pregnancy, or in the neonate. It is also seen in patients with cutaneous disorders such as burns or eczema. The most important factor in dissemination seems to be cell-mediated immune deficiency. The dissemination could be mucocutaneous, visceral or both. Sometimes, dissemination occurs in immunocompromised patients (e.g., AIDS) with acyclovir-resistant HSV infection. These patients respond to foscarnet therapy.<sup>92</sup> The incidence of systemic dissemination in autopsy studies has been found to be up to 6%. The esophagus is the most common organ involved, and patients present with odynophagia, dysphagia, retrosternal pain, weight loss, and fever. Other presentations of systemic involvement include monoarticular arthritis, hepatitis, thrombocytopenia, and myoglobinuria.

### EXTRAGENITAL LESIONS

Extragenital lesions are located mainly on the buttocks, groin or thigh. Rarely, fingertips or eyes can be involved. Majority of the extragenital lesions develop by autoinoculation of virus or by viral reactivation in another part of the affected dermatome. Extragenital lesions are principally thought to be due to autoinoculation into distant sites and not due to viremic spread.

### PELVIC INFLAMMATORY DISEASE (PID)

PID can occur due to both HSV-1 and HSV-2 as a result of local spread. It should be considered in a patient with primary genital herpes presenting with lower abdominal pain and adnexal uterine tenderness. Other causes should always be considered and excluded.

### SECONDARY MICROBIAL INFECTION

Bacterial superinfection is uncommon in immunocompetent patients. In contrast, vaginal fungal infection is frequently seen during the course of primary genital herpes, particularly in the 2nd week and characterized by a change in the vaginal discharge and re-emergence of vulval itching and irritation.

## Genital Herpes and HIV

Genital herpes is the most common STD in HIV seropositive individuals. Seventy percent of the HIV-positives in the developed world and 95% in the developing world have HSV-2 antibodies.<sup>93,94</sup> The frequency of HIV seropositivity in genital herpes patients has varied from 0.5% (1995) to 20% (1999)

in various parts of India.<sup>28–30</sup> In HIV-positive heterosexuals in south London, UK 43% of women and 38% of men had genital ulcers caused by HSV.<sup>95</sup> The seroprevalence of HSV-2 in USA has been 81% in HIV-positive homosexual and bisexual men.<sup>93</sup> The HIV and HSV co-infection in Haitian women is 88% and in CSWs from Zaire is 95%. In male factory workers in Zimbabwe, HSV-2 seroprevalence was 35.7% among HIV-negative subjects but 82.7% among HIV-positive subjects.<sup>96</sup> Recent studies have shown that HSV-2 infection increases the risk of HIV acquisition among women (threefold), heterosexual men (two-fold) and homosexual men (1.7-fold).<sup>97</sup>

### GENITAL HERPES FACILITATES HIV TRANSMISSION

The topic of interaction between various STIs and HIV is discussed elsewhere (see Chapter 84, “Sexually Transmitted Infections in HIV-Infected Patients”). In brief, epidemiological and biological evidence suggests enhanced HIV transmission in presence of genital ulcers due to genital herpes and other STIs. Genital ulcers may facilitate HIV transmission through the reduced epithelial barrier and infiltration of CD4+ lymphocytes in herpetic lesions that are possible targets for HIV attachment and entry.<sup>98</sup> HIV-1 virions can consistently be detected in genital ulcers caused by HSV-2, which suggests that genital herpes infection is likely to increase the efficiency of sexual transmission of HIV-1.<sup>99</sup> It is possible that the antigenic stimulation of mucosal sites by reactivation of HSV can increase HIV-1 replication on mucosal surfaces. HSV also accelerates the progression of HIV disease. Acute episodes of HSV infection can stimulate HIV replication with increased HIV viral RNA levels detectable in the plasma in individuals not on HAART.<sup>100,101</sup>

### HSV SUPPRESSION TO LIMIT HIV PROGRESSION

Suppressive antiviral therapy in HIV-infected people with detectable viral loads has been shown to decrease the levels of HIV viremia between  $\frac{1}{4}$  and  $\frac{1}{2}$  log.<sup>102</sup> Such a strategy will impact on the progression of HIV and potentially delay the need for antiretroviral treatment. A large RCT in early HIV (those individuals not on HAART and with CD4 counts above 250) has shown that standard doses of suppressive antiviral therapy (acyclovir 400 mg bd) will sustain CD4 counts above accepted treatment levels and this effect reduced the need for HAART at 2 years by 16% in the treatment group.<sup>103</sup>

### Clinical Manifestations

The severity of HSV infection increases in presence of immunosuppression. Necrotic ulceration may appear at unusual sites and more extensive and chronic lesions may occur (Fig. 28.8). Dissemination, both mucocutaneous and systemic, are more common in HIV seropositive individuals with HSV-2 infection. Esophagitis, pneumonitis, and hepatitis can occur. Vegetating (Fig. 28.9), verrucous or disseminated maculopapular eruptions can occur (*vide supra*).



**Fig. 28.9:** Vegetating long standing lesions of genital herpes in HIV seropositive patient. *Courtesy: DG Saple, Mumbai, India.*

## HSV Shedding in HIV Infection

Asymptomatic HSV shedding (or more appropriately, microrecurrences) occurs four times more commonly in HIV seropositive than in HIV seronegative women.<sup>104</sup> Asymptomatic perianal HSV shedding is also more commonly seen in HIV seropositive individuals.<sup>105</sup> An inverse correlation exists between the CD4 count and the rate of genital HSV-2 shedding and a direct correlation between plasma HIV RNA and shedding. Sub-clinical HSV shedding is almost certainly associated with cutaneous or mucosal ulceration, however, it may be clinically inapparent.<sup>106,107</sup>

## Laboratory Diagnosis of Genital HSV Infections

Despite the frequent occurrence of atypical disease genital herpes is often diagnosed on clinical grounds alone—most guidelines advise that where possible laboratory confirmation of the diagnosis should be attempted. This may also be necessary in a patient with predominantly asymptomatic disease.<sup>108</sup> The majority of patients with genital herpes may present with atypical lesions that are easily confused with other genital dermatoses. This is particularly the case in those with HIV infection. The success of laboratory diagnostic methods (Table 28.7) is dependent on a number of factors. Viral titers (higher in primary episodes, in the immunocompromised, and in early lesions), sampling technique, the use of appropriate specimens, transport, and the methodology selected.<sup>61</sup>

## COLLECTION OF SPECIMENS

HSV can be isolated from mucocutaneous genital lesions.

The sensitivity of culture greatly varies according to lesions chosen for specimen collection (Table 28.8).<sup>109</sup> For specimen collection, a large vesicle should be chosen and the fluid gathered onto a cotton-tipped swab, or a tuberculin syringe can be used

**Table 28.7:** Laboratory/Serological Techniques in the Diagnosis of Genital Herpes Infection

### 1. Laboratory techniques:

- (a) Viral culture
  - Isolation of the virus in cell culture
  - Allows for testing for antiviral susceptibility
  - Modified culture techniques
- (b) HSV direct detection tests
  - Cytology
  - Electron microscopy
  - HSV antigen detection
  - HSV *in situ* hybridization
  - HSV PCR

### 2. Serological techniques

- (a) Functional antibody assay
  - Neutralizing antibody assay
  - Complement fixation
- (b) Solid phase binding assays
  - Reverse passive hemagglutination
  - Indirect fluorescence antibody assay
  - Enzyme immunoassay
  - Antibody typing by IFA or EIA
- (c) Type-specific immunoassay
  - Protein-specific immunoassays
  - Western blot (immunoblot)

to aspirate the fluid.<sup>109</sup> If a large vesicle is not present, then the exudate of a small vesicle or open lesion is collected by vigorously rubbing with a cotton-tipped swab on a wire shaft. To collect cervical specimens, the swab should be taken from ectocervix and the entry of the endocervical canal, as HSV involves squamous rather than columnar epithelial cells. The specimen should be placed immediately into vials containing 1 ml of viral transport medium and should be kept at 4°C until cultured. Freezing of specimens is associated with a loss of culture isolation but is preferred to keeping samples for extended periods at 4°C and is advised if delays beyond 48 hours are anticipated.

## CULTURE

Isolation of HSV in cell culture was tillied; recently regarded as the “gold standard” for the diagnosis of acute HSV infections. Commonly used human diploid fibroblast lines such as MRC-5 are well-characterized for HSV growth and take 12–18 hours for HSV replication. Cytopathic effect (CPE) appears in 2–3 days after inoculation. Other viruses may exhibit a CPE similar to HSV. Thus isolates require confirmation.

The confirmatory tests are based on various methods like neutralization with type-specific antisera, immunological assays, such as immunofluorescence, and nucleic acid hybridization. HSV-1 and HSV-2 can be differentiated by using monoclonal antibodies directed to type-specific antigens in enzyme immunoassay (EIA) or fluorescence immunoassay. Advantages include high specificity and testing for antiviral susceptibility. However levels of viral shedding (e.g., in first vs. recurrent episodes and in early vs. late presentations) can significantly influence sensitivity. Delayed



**Table 28.8:** Sensitivity of Culture in Specimens Collected from Lesions at Different Stages

Nature of lesion	Sensitivity
Fresh vesicle (primary)	>90%
Pustular lesion (primary)	70–80%
Ulcerative lesion (primary)	70–80%
Recurrent infection	50%
Crusted lesion	25%

sample processing and lack of refrigeration after sample collection can decrease diagnostic yield.<sup>110,111</sup>

### HSV DIRECT DETECTION TESTS

Though cell culture techniques are highly sensitive, they may take many days for growth and confirmation of HSV. Negative results can take beyond a week. In many clinical situations a rapid diagnosis can be extremely helpful. Cytology, electron microscopy, and HSV antigen/DNA detection technique can be used for rapid HSV detection.

#### Cytology

It is 30–80% sensitive and is not routinely recommended for diagnosis (discussed earlier).

#### Electron Microscopy

It can be used for visualization of negatively stained HSV virions from vesicle fluid. The drawback of EM is, however, that it requires expensive equipment and trained personnel to perform the technique. Sensitivity is low and differentiation from other herpes virions is not possible.

### HSV Antigen Detection

- **Immunofluorescence:** Detection of HSV antigen can be done by binding of antibodies conjugated with fluorescent dyes (direct fluorescent antibody or DFA test). The sensitivity of DFA test for the detection of HSV in genital specimens varies between 70% and 90% of culture-positive specimens.<sup>109</sup> The technique requires a fluorescent microscope.
- **Immunoperoxidase (IP) tests:** Here, anti-HSV antibodies are conjugated with enzyme peroxidase and treated with the diaminobenzidine, which reacts with peroxidase enzyme to form a reddish brown complex in the sample where the antibody is bound to the viral antigen.
- **Enzyme immunoassay (EIA):** Two types of microtiter plate ELISA procedures for the direct detection of HSV antigens are available. (i) Antigen capturing: HSV antigen in clinical specimens is captured by polyclonal anti-HSV antibodies immobilized in microtiter plate walls. The im-

mobilized antigen is then treated with a biotin-labeled mouse monoclonal antibody. After adding streptavidin horseradish peroxidase conjugate and chromogenic substrate, a colored reaction product is obtained. (ii) Antigen–antibody amplification: Specimens are added to wells coated with mouse monoclonal antibody and an alkaline phosphatase conjugate. HSV antigen present in the specimens will react with the antibody and become immobilized. The bound enzyme is then treated with a substrate giving a colorless product, which is then treated with an amplifier. This produces a colored reaction product. The sensitivity of ELISA is 70–95% and specificity is 94–100% for symptomatic patients and offers a rapid diagnostic tool in settings with limited laboratory facilities.

- **Rapid assay:** HSV antigen is extracted from the clinical specimen with a buffered solution. The extract is added to a test device and any antigen present is immobilized on a membrane. When treated with peroxidase-labeled anti-HSV monoclonal antibody with a substrate, a colored spot is obtained on the membrane. Inability to type HSV is a severe limitation of ELISA.

### HSV-DNA Detection (DNA Hybridization)

The sensitivity of this test is equal to that of HSV antigen detection tests in symptomatic HSV infection but not in asymptomatic HSV infections. The detection of HSV by DNA hybridization is done using radiolabeled or biotin-labeled probes.

### HSV-PCR

HSV DNA detection by real-time PCR increases HSV detection rates in mucocutaneous swabs by 11–71% compared with virus culture and is recommended as the preferred diagnostic method.<sup>112–114</sup> Real-time PCR can tolerate less stringent conditions for sample storage and transport than virus culture, and allows the rapid detection and typing of HSV with a lower risk of contamination than traditional PCR assays. Compared to culture PCR is better for early and late presentations as well as those with initial or recurrent disease. A particular benefit is that a negative result is available within a few hours if required.

### Serological Testing

Serological testing is not routinely recommended in asymptomatic patients but is indicated in the following groups<sup>115–121</sup>:

- History of recurrent or atypical genital disease when direct virus detection methods have been negative. HSV-2 antibodies are supportive of a diagnosis of genital herpes; HSV-1 antibodies do not differentiate between genital and oropharyngeal infection.
- First-episode genital herpes, where differentiating between primary and established infection guides counseling and management. At the onset of symptoms, the absence of HSV



IgG against the virus type detected in the genital lesion is consistent with a primary infection.<sup>115</sup> Seroconversion should be demonstrated at follow-up.

- Sexual partners of patients with genital herpes, where concerns are raised about transmission. Serodiscordant couples can be counseled about strategies to reduce the risk of onward transmission.
- Testing of asymptomatic pregnant women is not routinely recommended, but is indicated when there is a history of genital herpes in the partner.<sup>122–124</sup> HSV-1 and/or HSV-2 seronegative women should be counseled about abstinence or at least avoiding unprotected sex in the last trimester to avoid acquisition of either virus type during pregnancy.

Limited data suggest an increased risk of perinatal HIV transmission among HSV-2 seropositive HIV-infected women.<sup>125,126</sup> As evidence is not consistent, testing of HIV-positive pregnant women is not routinely recommended.<sup>127</sup>

HSV serological assays should be used that detect antibodies against the antigenically unique glycoproteins gG1 and gG2.<sup>128,129</sup> Non-type-specific HSV antibody assays are of no value in the management of genital herpes. The main utility of these commercially developed serological methods is the identification of undiagnosed HSV-2 infection.

Western blot (WB) is the diagnostic gold-standard. It is >97% sensitive and >98% specific, but is labor-intensive and not commercially available.<sup>130,131</sup>

Several commercial (e.g., Focus HerpeSelect ELISA and Immunoblot; Kalon HSV-2 assay) and in-house assays are available, with reported sensitivities >95% and generally high specificities. False negative results are more likely to occur in early infection and can be resolved by repeat testing. False positive results have been observed in populations with low prevalence and in some African cohorts.<sup>132</sup> Rapid point of care tests are available (e.g., Biokit HSV-2 assay, previously POCKIT™ HSV-2, with sensitivity and specificity >92%) and new assays are being developed.<sup>133</sup>

HSV seroprevalence rates, presence of risk factors for genital herpes, and clinical history influence the positive predictive value (PPV) of HSV type-specific serology and should guide testing and result interpretation. Type-specific HSV IgG becomes detectable 2 weeks to 3 months after the onset of symptoms and is commonly negative in early presentations.<sup>126</sup> Where clinically indicated, follow-up samples should be taken to demonstrate seroconversion. Paired serology combined with virus isolation can be used for disease classification (Table 28.4). HSV IgM testing substantially increases the ability to detect early infection in patients who lack detectable IgG,<sup>134</sup> however has limited availability in routine diagnostic settings. In addition, IgM testing can also be positive during reactivation of disease and negative during primary disease, and is not viral-type specific. Because of these limitations, the test cannot be recommended in routine clinical practice.

## Treatment

### DRUGS

#### Acyclovir

Acyclovir is a white crystalline powder soluble in water.<sup>135</sup> It is highly active against HSV-1, slightly less active against HSV-2 and approximately eightfold less active against the varicella zoster virus. It is also active against Epstein–Barr virus and human herpes virus-6, but not against cytomegalovirus. The antiviral activity of acyclovir is due to intracellular conversion of acyclovir, by viral thymidine kinase, to the monophosphate with subsequent conversion by cellular enzymes to the diphosphate and the active triphosphate. This active form inhibits viral DNA synthesis and replication by inhibiting the herpes virus DNA polymerase enzyme as well as by being incorporated into the viral DNA. The whole process is highly selective for infected cells. Acyclovir has no activity against latent virus, but it inhibits latent HSV at an early stage of reactivation.

#### Adverse Effects

The most frequent adverse effects of acyclovir reported during clinical trials were nausea, vomiting, and headache. Serious adverse drug reactions and cumulative toxicity are rare although renal crystallization and neutropenia have been reported.

#### Resistance<sup>136</sup>

HSV develops resistance to acyclovir *in vitro* and *in vivo* by selection of mutants deficient in thymidine kinase. Other mechanisms of acyclovir resistance include altered substrate specificity of thymidine kinase and reduced sensitivity of viral DNA polymerase. Although, there have been many reports of treatment failure, resistance has never been a major problem in genital herpes. This can be explained on the basis of low incidence of resistant mutants *in vivo* and because viruses deficient in thymidine kinase generally appear to be of diminished virulence with reduced infectivity and latency. Resistant viruses are most troublesome in immunocompromised patients. HSV resistant to acyclovir because of absence of thymidine kinase may be cross-resistant to other antivirals phosphorylated by this enzyme, such as brivudine, idoxuridine, and ganciclovir. Viruses resistant due to altered substrate specificity of thymidine kinase may also be resistant to brivudine.

#### Pharmacokinetics

Acyclovir can be administered in oral, intravenous or topical formulations.<sup>137</sup> The bioavailability after oral administration is only 15–30% and a 200 mg oral dose results in a peak plasma concentration of 0.4–0.8 mg/mL approximately 1.5 hour after administration. The plasma half-life is 2.1–3.5 hours in patients with normal renal function. It is eliminated largely unmetabolized by the renal route. In patients with compromised renal function, the dosage should be reduced. With 5% acyclovir ointment in

polyethylene glycol base, application results in detectable drug concentrations in the lesion.

### Acyclovir in Pregnancy

Acyclovir is not teratogenic in the mouse or rabbit.<sup>138,139</sup> In non-standard tests in which the drug was given in rats for only 1 day during the period of major organogenesis, fetal abnormalities, such as head and tail abnormalities, were observed, and was associated with toxicity to the maternal rat.<sup>140</sup> The clinical relevance of these experiments is unknown. The acyclovir in pregnancy register has now been closed but in its final report data on 1129 pregnancies is reported. This shows the incidence of congenital anomalies and fetal loss did not appear to be higher than the general population.<sup>138</sup> Transient neutropenia in some neonates of questionable significance has been reported in a third trimester treatment study.<sup>141</sup> Acyclovir is excreted in breast milk following oral administration. Although most formularies advise caution to be exercised when prescribing to breastfeeding mothers it is generally considered a safe drug.<sup>135</sup>

### Famciclovir/Penciclovir

Like acyclovir, penciclovir is an acyclic guanosine analog and inhibits HSV DNA synthesis by short-chain termination. Penciclovir is poorly absorbed orally, but is active intravenously. Its diacetate ester, famciclovir, developed for oral use, is converted, after absorption, in the intestinal wall and liver, to the active compound, penciclovir. Penciclovir is eliminated unchanged by the liver. The plasma half-life for penciclovir is identical to that of acyclovir (2.5 hour). The initial phosphorylation to penciclovir monophosphate is carried out by HSV-induced thymidine kinase (like acyclovir). Phosphorylation to di- or tri-phosphate forms is carried out by cellular kinases. Penciclovir triphosphate has antiviral activities against HSV-1, HSV-2, VZV, EBV, and hepatitis B virus. It inhibits viral DNA polymerase. There are some quantitative differences in the mechanisms of action between penciclovir and acyclovir. Compared with acyclovir, penciclovir is preferentially taken up and phosphorylated by HSV and VZV infected cells. Penciclovir triphosphate has a very prolonged intracellular half-life in infected cells (7–20 hours vs. 0.7–1 hour for acyclovir triphosphate). However, more penciclovir triphosphate is required for inhibition of HSV DNA polymerase compared with acyclovir triphosphate.<sup>142</sup> Studies in mice have shown that famciclovir (which is converted into penciclovir after absorption) has different effects on the course of the disease when compared with acyclovir and valacyclovir. In mice with experimentally produced first episode of genital herpes, immediately after stopping valacyclovir, the disease recurred, while famciclovir resulted in a prolonged suppression with no recurrences.<sup>143</sup> However, these effects have not been confirmed in humans.<sup>144</sup> and a single study in first episodes of herpes comparing high-dose famciclovir to standard therapy with other antivirals showed no impact on the natural history of the disease. The majority of acyclovir-resistant HSV clinical isolates will also

be resistant to penciclovir.<sup>105</sup> Randomized placebo controlled trials of famciclovir in the treatment of active recurrent genital herpes have demonstrated that 125, 250 or 500 mg twice daily doses of famciclovir reduce the duration of viral shedding, time required for appearance of crusting, time required for complete healing and duration of symptoms.<sup>105</sup> In a randomized controlled trial, oral famciclovir in dosages of 125 or 250 mg, three times daily, or 250 mg twice daily given for 52 weeks was found safe, effective and well-tolerated.<sup>145</sup> Oral famciclovir has also been used successfully for suppression of recurrences in genital herpes with frequent episodes.<sup>142</sup>

### Adverse Effects

Famciclovir is a well-tolerated drug and serious side effects are uncommon. Prolonged, high-dose administration of famciclovir to rats was associated with an increased incidence of mammary adenocarcinomas in female rats. The clinical significance of this is unknown. Testicular toxicity was observed in rats, mice, and dogs following repeated administration of famciclovir or penciclovir. These effects were only noted at doses higher than those used in human studies and long-term studies in healthy males have shown no impact on sperm function. There is limited data of its use in pregnancy.

### Valacyclovir

Valacyclovir, a prodrug of acyclovir (L-valyl ester of acyclovir), was developed mainly to improve its bioavailability. Oral valacyclovir is rapidly absorbed and almost completely converted to acyclovir in the intestine and liver. Oral valacyclovir results in a 3–5-fold greater bioavailability (15–30% for acyclovir vs. 54% for valacyclovir<sup>146</sup>). The pharmacokinetics and toxicity of valacyclovir are comparable to that of acyclovir. Thrombotic microangiopathy has been observed in about 3% of immunocompromised patients receiving 8 g/day of valacyclovir for prevention of CMV disease. This, however, has not been observed for lower doses used for varicella or HSV infection.<sup>147</sup> Two placebo-controlled comparative trials of acyclovir and valacyclovir have shown no difference in efficacy of both the drugs in recurrent genital herpes. The dosages of valacyclovir used in these studies were 1000 and 500 mg twice daily and 200 mg of acyclovir five times a day with no difference in the outcome. The only advantage found with valacyclovir was its convenient bid dosing.<sup>148,149</sup> Valacyclovir (500 mg once daily) has also been shown to suppress recurrent genital herpes. Valacyclovir has been used to suppress patients with, severe (>10 episodes a year), moderate and mild disease as well as those with only serologically apparent disease—all these trials again confirm efficacy.<sup>150–152</sup>

### Ganciclovir

It is a nucleoside analog that is similar in structure to acyclovir. However, it is more active against CMV. It has good activity against HSV-1, HSV-2, VZV, and EBV and is also active

against HHV-6 and HBV. The drug is discussed elsewhere (See Chapter 33, “Human Cytomegalovirus Infection”).

### Idoxuridine

It is a nucleoside analog, active against HSV-1, HSV-2, VZV, and poxviruses.<sup>101</sup> It is converted into idoxuridine triphosphate, which inhibits viral DNA polymerases and also acts as a chain terminator. It is available as 1% ophthalmic solution in distilled water and as a 0.5% ophthalmic ointment in a petrolatum base. It is approved for treatment of HSV keratitis. Idoxuridine in DMSO has been reported to have beneficial effects on mucocutaneous HSV infections.<sup>153</sup> Systemic use has been abandoned because of toxicities.

### Trifluridine

It is a pyrimidine nucleoside analog with activity against HSV-1, HSV-2, CMV, and vaccinia.<sup>154</sup> Topical trifluridine, either alone or in combination with interferon, has been reported to be beneficial in the treatment of acyclovir-resistant mucocutaneous HSV infections in patients with AIDS.

### Cidofovir

This is an acyclic nucleoside phosphonate, which unlike acyclovir, is phosphorylated only by cellular enzymes.<sup>155</sup> Hence, it is active against HSV with deficient or altered thymidine kinase enzyme. Topical and i.v. cidofovir have been successfully used for the treatment of acyclovir-resistant HSV lesions in AIDS or marrow transplantation patients.<sup>156</sup> A double blind placebo controlled trial of topical 0.3% or 1% cidofovir gel in 30 patients with AIDS who did not respond to acyclovir therapy showed that lesions healed by at least 50% in 50% of patients who received cidofovir.<sup>157</sup> As the i.v. administration of cidofovir is associated with systemic side effects, in particular renal toxicity, topical therapy is preferred.

### Foscarnet

It is a phosphonate viral DNA polymerase inhibitor. Intravenous administration is associated with systemic toxicity. Foscarnet has been the preferred agent for patients with acyclovir-resistant HSV infection. In one study of 26 patients with acyclovir-resistant HSV infection the lesions healed in 81% of the patients with foscarnet.<sup>158</sup> The most common toxicities are renal insufficiency and metabolic disturbances (mainly hypophosphatemia). HSV resistance to foscarnet can occur after prolonged use.<sup>159</sup> In such a situation, the addition of acyclovir to the treatment regimen may be beneficial.<sup>155</sup>

### Other Drugs

**n-Docosanol:** This is also known as behenyl alcohol. It is produced by high pressure, catalytic hydrogenization of a mixture of fatty acids derived from extracts of various plant sources. 10% cream of n-Docosanol has been found to be effective in recurrent HSV infection in experimental models.

**Imiquimod and resiquimod:** Case reports of these agents suggest some limited value in managing HSV infection. Such effects have not been clearly demonstrated in well-controlled studies.

**Isoprinosine:** This agent was widely promoted as improving the hosts own immune control of HSV. A head-to-head study compared Isoprinosine to Acyclovir and placebo and found that over a 6 month period the studied dose (Isoprinosine 500 mg twice daily) had no therapeutic value.<sup>160</sup>

**Helicase primase inhibitors:** A number of orally available agents have been identified that interfere with the activity of the helicase primase complex at key stages of DNA replication.<sup>161</sup> Development to date has demonstrated that these agents in the laboratory can be extremely powerful inhibitors of HSV replication. However, work to date has not yielded clinically useful compounds. Phase two studies are currently underway with newer agents in this family of drugs.

## CLINICAL MANAGEMENT

### Management of First Episode

Patients presenting early in the disease (within 5 days of the start of the episode or while new lesions are still forming), patients who have systemic symptoms, complications or are immunocompromised should be given oral antivirals (Table 28.9).<sup>162,163</sup> Acyclovir, valacyclovir, and famciclovir reduce the severity, viral shedding, itching, average healing time and frequency of new lesion formation during the acute episode.<sup>164</sup> Antiviral therapy, however, does not alter the long-term natural history of the disease. The duration of treatment varies in different recommended treatment guidelines (Table 28.9) with a range of 5–10 days, however there are no comparative studies available. Since acquisition episodes can occasionally be prolonged it would be advisable to continue therapy while new lesions are forming or the patient remains systemically unwell. Intravenous acyclovir should be considered when the patient is unable to swallow, when oral administration may not guarantee absorption (e.g., vomiting) and if severe complications such as neurological disease or dissemination is occurring when guaranteed delivery of the agent is essential and levels that are higher than may be achieved orally are required.<sup>162</sup> Symptomatic/supportive treatment in the form of bathing in salt water (e.g., half a cup of ordinary household salt in the bath) will help relieve the pain. Topical anesthetic jelly can be used; however, there is a theoretical risk of sensitization although this is unlikely over the short duration for which it is recommended. Analgesics should also be offered. During an acquisition episode the patient will be developing a full immune response but does remain vulnerable to further inoculation of the virus at distant sites. Advice on washing hands carefully after treating lesions and the use of a separate towel for the genital area is often given.

### Management of Recurrent Genital Herpes

Recurrences of genital herpes generally cause minor symptoms, which are self limiting. For most patients, supportive therapy in



**Table 28.9:** Guidelines for Management of Genital Herpes

<b>(a) First episode</b>	
(i) CDC guidelines 2010	<ul style="list-style-type: none"> <li>Acyclovir 400 mg orally, three times a day for 7–10 days, or</li> <li>Acyclovir 200 mg orally, five times a day for 7–10 days, or</li> <li>Famciclovir 250 mg orally, three times a day for 7–10 days, or</li> <li>Valacyclovir 1 g orally, two times a day for 7–10 days</li> </ul>
(ii) UK National guidelines 2007	<ul style="list-style-type: none"> <li>Acyclovir 200 mg orally, five times a day for 5 days, or</li> <li>— Acyclovir 400 mg orally, three times a day for 5 days, or</li> <li>Famciclovir 250 mg orally, three times a day for 5 days, or</li> <li>Valacyclovir 500 mg orally, two times a day for 5 days</li> </ul>
(iii) IUSTI/WHO European guidelines 2010	<ul style="list-style-type: none"> <li>Acyclovir 200 mg orally, five times a day for 5 days, or</li> <li>Acyclovir 400 mg orally, three times a day for 5 days, or</li> <li>Famciclovir 250 mg orally, three times a day for 5 days, or</li> <li>Valacyclovir 500 mg orally, two times a day for 5 days</li> </ul>
(iv) Australian guidelines (AHMF) 2007	<ul style="list-style-type: none"> <li>Acyclovir 200 mg orally, five times a day for 10 days, or</li> <li>Acyclovir 400 mg orally, three times a day for 7–10 days, or</li> <li>Famciclovir 250 mg orally, three times a day for 7–10 days, or</li> <li>Valacyclovir 500 mg orally, two times a day for 5–10 days</li> </ul>
<b>Episodic therapy for recurrent genital herpes</b>	
(i) CDC guidelines 2010	<ul style="list-style-type: none"> <li>Acyclovir 400 mg orally, three times a day for 5 days, or</li> <li>Acyclovir 800 mg orally, two times a day for 5 days, or</li> <li>— Acyclovir 800 mg orally, three times a day for 2 days, or</li> <li>Famciclovir 125 mg orally, two times a day for 5 days, or</li> <li>— Famciclovir 1000 mg orally, two times a day for 1 day, or</li> <li>— Famciclovir 500 mg once followed by 250 mg twice daily for 2 days</li> <li>Valacyclovir 500 mg orally, two times a day for 3 days, or</li> <li>Valacyclovir 1.0 g orally, once a day for 5 days</li> </ul>
(ii) UK National guidelines 2007	<ul style="list-style-type: none"> <li>Acyclovir 200 mg orally, five times a day for 5 days, or</li> <li>Acyclovir 400 mg orally, three times a day for 3–5 days, or</li> <li>Acyclovir 800 mg orally, three times a day for 2 days, or</li> <li>Famciclovir 125 mg orally, two times a day for 5 days, or</li> <li>Famciclovir 1.0 g orally, two times a day for 1 day, or</li> <li>Valacyclovir 500 mg orally, two times a day for 5 days, or</li> <li>Valacyclovir 500 mg orally, two times a day for 3 days</li> </ul>
(iii) IUSTI/WHO European guidelines 2010	Same as UK guidelines 2007
(iv) Australian guidelines (AHMF) 2007	<ul style="list-style-type: none"> <li>Acyclovir 200 mg orally, five times a day for 5 days, or</li> <li>Acyclovir 800 mg orally, two times a day for 5 days, or</li> <li>Famciclovir 125 mg orally, two times a day for 5 days, or</li> <li>Valacyclovir 500 mg orally, two times a day for 5 days</li> </ul>
<b>(b) Suppressive therapy for recurrent genital herpes (for recurrence rate &gt; 6 per year, the effect of therapy should be assessed after completion of 1 year)</b>	
(i) CDC guidelines 2010	<ul style="list-style-type: none"> <li>Acyclovir 400 mg orally, two times a day, or</li> <li>Famciclovir 250 mg orally, two times a day, or</li> <li>Valacyclovir 500 mg orally, once a day, or</li> <li>Valacyclovir 1.0 g orally, once a day</li> </ul>
(ii) UK National guidelines 2007	<ul style="list-style-type: none"> <li>Acyclovir 200 mg orally, four times a day, or</li> <li>Acyclovir 400 mg orally, two times a day, or</li> <li>Famciclovir 250 mg orally, two times a day, or</li> <li>Valacyclovir 500 mg orally, once a day</li> </ul>

(iii) IUSTI/WHO European guidelines 2010

- Acyclovir 200 mg orally, four times a day, or
- Acyclovir 400 mg orally, two times a day, or
- Valacyclovir 500 mg orally, once a day (for <10 recurrences/year)
- Valacyclovir 250 mg orally two times a day or 1.0 g orally once a day (for >10 recurrences/year)

(iv) Australian guidelines (AHMF) 2007

- Acyclovir 200 mg orally, 2–3 times a day (considered in pregnancy), or
- Acyclovir 400 mg orally, two times a day, or
- Famciclovir 250 mg orally, two times a day, or
- Valacyclovir 250 mg orally two times a day or 500 mg orally once a day (for <10 recurrences/year), or
- Valacyclovir 1.0 g orally once a day (for >10 recurrences/year)

**(c) Genital herpes in HIV infected individuals (and other immunocompromised states)**

(i) CDC guidelines 2010

For episodic therapy:

- Acyclovir 400 mg orally, three times a day for 5–10 days, or
- Famciclovir 500 mg orally, two times a day for 5–10 days, or
- Valacyclovir 1.0 g orally, two times a day for 5–10 days

For suppressive therapy

- Acyclovir 400–800 mg orally, 2–3 times a day, or
- Famciclovir 500 mg orally, two times a day, or
- Valacyclovir 500 mg orally, two times a day

(ii) UK National guidelines 2007

- Episodic and Suppressive regimes-same as CDC 2010,
- For resistant genital herpes-active lesions:
- Standard aciclovir therapy, if unresponsive,
- Acyclovir 800 mg five times a day, if still unresponsive,
- Topical trifluridine 8 hourly until complete healing (for accessible lesions), or
- IV foscarnet 50 mg/kg twice daily until complete healing (for inaccessible lesion)

(iii) IUSTI/WHO European guidelines 2010

Episodic therapy:

- Acyclovir 200–400 mg orally, five times a day, or
- Acyclovir 400–800 mg orally, three times a day, or
- Famciclovir 250–500 mg orally, three times a day, or
- Valacyclovir 500 mg–1.0 g orally, two times a day

Suppressive therapy:

- Acyclovir 400 mg orally, two times a day, or
- Valacyclovir 500 mg orally, two times a day, or
- Famciclovir 500 mg orally, two times a day

(iv) Australian guidelines (AHMF) 2007

Episodic:

- Valacyclovir 500 mg orally, two times a day for 5–10 days, or
- Famciclovir 500 mg orally, two times a day for 5–10 days

Suppressive:

- Valacyclovir 500 mg orally, two times a day, or
- Famciclovir 500 mg orally, two times a day

the form of simple analgesics, saline bathing and topical occlusion with petroleum jelly or a dry dressing is sufficient. Episodic antiviral therapy (oral acyclovir/valacyclovir/famciclovir) will reduce the duration and severity of the episode although in large studies the average reduction in duration is only by a median of 1–2 days and is only present when therapy is initiated early in the evolution of the recurrence.<sup>165–167</sup> Episodic therapy to be effective



must be initiated by patients at the first signs of a recurrence.<sup>167</sup> Although the newer antiviral agents (famciclovir and valacyclovir) have not been shown to be clinically superior to acyclovir in 5 days studies of episodic therapy,<sup>144,168</sup> a large body of work now shows that high-dose therapy with prodrugs over short durations, even down to 1–2 days is as effective as 5 days of therapy and significantly better than placebo in generating aborted lesions (lesions that do not progress beyond the prodromal to papular stages).<sup>168–173</sup> An impact on lesion abortion better than placebo has also been demonstrated with Acyclovir 800 mg tds when used for 2 days.<sup>174</sup> These studies all support the use of patient initiated, high dose, short episodes of therapy over the traditional longer 5 days courses.

**Suppressive therapy:** Daily antiviral therapy effectively suppresses recurrences. Prices for generic equivalents have in recent years fallen dramatically and most decisions around the initiation of therapy can now be based on clinical effectiveness and inconvenience for the patient. In assessing a patient for suppressive therapy it is important to assess not just the disease frequency (e.g., >6 recurrences/yr), the severity of each episode including the presence of disturbing prodromes, as well the greater effects that the disease has on the patient such as psychological and psychosexual impacts.<sup>163</sup> Suppressive regimens of antiviral medication decrease the frequency of genital herpes recurrences by up to 80% and 25–30% patients who receive suppressive therapy experience no further recurrences while on therapy.<sup>134</sup> One multi-centric 5-year trial of suppressive therapy with acyclovir in 1100 immunocompetent patients with >12 recurrences per year showed a reduction in the recurrence rate from 12.9 at baseline to 0.8 in year 5; 20% of the patients were recurrence free for all 5 years.<sup>137</sup> No significant adverse reactions were noted. Suppressive therapy has been shown in well-conducted studies to improve psychological well-being in patients with HSV. Suppressive therapy also decreases asymptomatic shedding by 85%<sup>175</sup> and has been shown to effectively prevent the sexual transmission of HSV to uninfected partners—the only large study that has looked at this in serodiscordant couples found that continuous suppressive valacyclovir in those with recurrent disease of less than 10 episodes/yr reduces transmission by approximately 50% in an 8 month follow-up period.<sup>120,176</sup>

**Convenience and cost.** Valacyclovir can be administered in once daily dosages,<sup>177,178</sup> and offers some advantage over acyclovir and famciclovir. Patients receiving suppressive therapy should be advised that antiviral therapy does not cure the underlying infection or completely halt asymptomatic viral shedding.<sup>179,180</sup>

**Safety.** Acyclovir has been used extensively for the last two decades for long-term suppression. A small cohort of patients has used it daily for over 10 years. While such long-term administration is not necessary in the majority of the patients, it is encouraging that the drug is well-tolerated.<sup>181,182</sup> Similarly experience with long-term use of both valacyclovir and famciclovir has also grown and both agents have good long-term safety records (more data is available for valacyclovir since this has been much more widely used). Decisions to discontinue suppressive

therapy once it has been initiated should be made jointly with the patient—most clinicians would not give suppressive therapy for a period of less than 6 months in the first instance although short duration therapy to cover a specific time period of concern for the patient is often valuable.

## Genital Herpes in HIV Infected Individuals (as well as Other Patients in Immunocompromised States)

Patients with HIV infection have more frequent and prolonged episodes with slower responses to acyclovir, even in the absence of overt acyclovir resistance. There is a substantial increase in the rate of subclinical shedding.<sup>104</sup> One double blind, placebo control trial of famciclovir in HIV-infected persons with genital HSV infection (dose 500 mg twice daily for 8 weeks) has shown significant reduction in symptoms associated with HSV infection and the symptomatic and asymptomatic shedding of HSV.<sup>183</sup> A study comparing suppressive therapy with acyclovir and valacyclovir revealed that both drugs are equally effective in suppressing the genital HSV in HIV-infected patients.<sup>184</sup> Studies do however show that twice daily therapy is superior in this group to once daily treatments.

The evidence base to make recommendations for therapy in this group is relatively limited and for many patients the general adage to double the dose of a drug and to give it for longer may not be necessary.<sup>185</sup>

The frequency of acyclovir resistance in HIV-infected patients appears low.<sup>157</sup> With the decline of HSV culture facilities, *in vitro* testing of HSV isolates for acyclovir susceptibility is extremely difficult to source. Genotypic assessment of HSV strains can yield some useful information about their susceptibility to different therapies but such determination is unreliable and presently only available in select research settings. HIV-positive patients with persistent HSV infection, unresponsive to high-dose acyclovir, should be tested for resistance.<sup>157,162</sup> Patients unresponsive to acyclovir therapy are often also resistant to valacyclovir and famciclovir—they can be treated with topical trifluridine 8 hourly or IV foscarnet 50 mg/kg twice daily until complete healing.<sup>127</sup> Every effort must be made to improve the patient's immune status to reduce the rate of recurrences needing multiple courses of acyclovir which could potentially result in development of ACV-resistant strains.

## HSV Latency and Antiviral Therapy

HSV latency is responsible for recurrences and persistent infection and is the main hurdle in the search for a true therapeutic “cure” for the disease.<sup>186</sup> Experimental studies in animals have shown that it is possible to limit the magnitude of latency (i.e., the number of latently infected neurons) by prompt administration of nucleoside analogs and helicase primase inhibitors to such an extent that subsequent recurrences may be less frequent. Human studies with high-dose therapies (intravenous acyclovir and prodrugs) have not been able to show such an effect; this

may be due to the late stages at which most patients present. A recent study of a vaginally administered antiviral (tenofovir)<sup>187</sup> showed that regular use in those at high risk of HSV diminished acquisitions by half.

### Effect of Antivirals on Asymptomatic Shedding

Controlled trials have shown a significant suppression of asymptomatic viral shedding with acyclovir suppressive therapy. One such trial showed that patients on suppressive therapy with acyclovir had asymptomatic shedding on 0.3% of days, in contrast, patients on placebo showed asymptomatic shedding on 6.9% of days when assessed by culture.<sup>180</sup> Similar trials with valacyclovir showed a decline in viral shedding from 15.3% of days in the placebo group to 0.7% of days in valacyclovir group.<sup>188</sup> Head-to-head studies between all antivirals have not been completed and where available the data often is from only one study. Current evidence indicates that suppressive antiviral therapy can reduce infectivity in most groups. Clinically, an impact on transmission has only been demonstrated with valacyclovir in the context of established serodiscordant heterosexual relationships outside of pregnancy.<sup>120</sup> However, many guidelines recommend the extension of this finding to many other groups.<sup>189</sup>

### Management of Genital Herpes in Pregnancy

Women with genital herpes infection in pregnancy are at risk of transmitting herpes to their baby at the time of delivery resulting in neonatal herpes infection. Over 95% of infected babies are born to women who are unaware that they have genital herpes. Neonatal herpes is a severe illness with a high mortality and morbidity even with prompt antiviral treatment.<sup>190,191</sup> According to IUSTI/WHO European guidelines 2010, following considerations should be taken into account for the management of pregnant women with first episode genital herpes.<sup>162</sup>

#### FIRST AND SECOND TRIMESTERS ACQUISITION

A significant risk of miscarriage is present. Management of the woman should be in line with her clinical condition and will often involve the use of either oral or intravenous acyclovir in standard doses. Providing that delivery does not ensue, the pregnancy should be managed expectantly and vaginal delivery anticipated. Daily suppressive acyclovir 400 mg tid from 36 weeks gestation may prevent HSV lesions at term and hence the need for delivery by Caesarean section.<sup>192–197</sup>

#### THIRD TRIMESTER ACQUISITION

Caesarean section should be considered for all women, particularly those developing symptoms within 6 weeks of delivery, as the risk of viral shedding in labor is very high. Daily suppressive aciclovir 400 mg tid from 36 weeks gestation may prevent HSV lesions

at term. If vaginal delivery is unavoidable, prolonged rupture of membranes and invasive procedures, including the use of scalp electrodes, should be avoided. Intrapartum IV acyclovir given to the mother and subsequently to the baby may be considered and the pediatrician should be informed.<sup>198</sup>

### MANAGEMENT OF PREGNANT WOMEN WITH RECURRENT GENITAL HERPES

Women with recurrent genital herpes should be informed that the risk of neonatal herpes is low. Symptomatic recurrences of genital herpes during the third trimester will be brief; vaginal delivery is appropriate if no lesions are present at delivery. For women with a history of recurrent genital herpes who would opt for a Caesarean section if they had HSV lesions at the onset of labor, daily suppressive acyclovir 400 mg tid from 36 weeks gestation may prevent HSV lesions at term and hence the need for delivery by Caesarean section.<sup>151,199</sup> If there are no genital lesions at delivery, there is no indication for a Caesarean section to prevent neonatal herpes. Sequential cultures or PCR during late gestation to predict viral shedding at term are not indicated.<sup>200</sup> The utility of taking cultures or PCR at delivery, in order to identify women who are asymptotically shedding HSV is unproven. Management of women with genital lesions at onset of labor Caesarean section may be considered for women with recurrent genital herpes lesions at the onset of labor but the risk of neonatal herpes following vaginal delivery is small and must be set against risks to the mother of Caesarean section. Evidence from the Netherlands shows that a conservative approach, allowing vaginal delivery in the presence of an anogenital lesion, has not been associated with a rise in numbers of neonatal HSV cases.<sup>201</sup> However, this approach can only be adopted if fully supported by obstetricians and neonatologists, and if consistent with local medico-legal advice. Clinical diagnosis of genital herpes at the time of labor correlates relatively poorly with HSV detection from genital sites by either culture or PCR and fails to identify women with asymptomatic HSV shedding.

### Management of Psychosocial Sequelae of HSV Infection

Many studies have suggested that there is a psychological morbidity associated with recurrent infection, which is not necessarily attributable to the physical restriction that frequently recurring infection may impose.<sup>202–205</sup> At the time of diagnosis, patients may experience anguish, helplessness, feelings of depression or rage (self-directed or focussed on the person who is suspected of transmitting the infection or on the diagnosing physician) and reduced self-esteem.<sup>206–209</sup> Patients with recurrent genital herpes may experience shame and guilt or withdraw from social interactions and intimate relationship because of concerns about undesirability, discovery, disapproval and rejection, leading to increasing isolation and withdrawal.<sup>210,211</sup> For most patients a diagnosis of genital herpes is often their first diagnosis of a chronic long-term condition and they will often consider it the worst

thing that has happened to them.<sup>212</sup> The physician should not be dismissive of the patient's disease and care should be taken to provide adequate, appropriate and timely support and counseling.

Counseling of patients should include a discussion on the following points:

- (a) Possible source(s) of infection
- (b) Natural history including risk of subclinical viral shedding
- (c) Future treatment options
- (d) Risk of transmission by sexual and other means
- (e) Risks of transmission to the fetus during pregnancy and the advisability of the obstetrician/midwife being informed
- (f) Sequelae of infected men infecting their uninfected partner during pregnancy

Antiviral suppression is an effective way to improve and manage psychosexual problems. There will be a small group of patients who will not adjust to their diagnosis, remain socially withdrawn and develop clinically significant depression or obsessive rumination concerning their disease. Timely referral for formal psychological support should be considered in these cases. It is widely advised that episodic therapy may aggravate psychosexual problems because of the need for patients to be constantly aware of the possible need to instigate therapy at the earliest sign of any symptoms.

## Vaccines

Many types of vaccines against HSV have been developed in an attempt to prevent acquisition or to modify the frequency and/

or severity of recurrences<sup>213,214</sup> (Table 28.10). Numerous forms of non-specific immune stimulation like BCG vaccine, levamisole, and vaccinia inoculation have been tried.<sup>8</sup> In animal studies, vaccine-induced immunity has failed to prevent viral replication in the genital tract and establishment of latent infection in sensory ganglia after experimental HSV challenge.<sup>215–217</sup> In spite of failure to provide sterilizing immunity and protect against infection, vaccines in experimental models do protect animals from developing severe clinical manifestations and acquisition episodes are milder. These studies also show that it is possible with vaccination to reduce the magnitude and duration of viral replication as well as the burden of latent infection within neurones.<sup>215</sup> The frequency of recurrences is also lower in vaccinated animals. The precise role of vaccines in future management of HSV disease is yet to be defined.<sup>213</sup> It is unlikely that vaccines will give complete protection, but partial protection is a realistic goal. Vaccines may also have a place in prevention of disseminated neonatal HSV infection. To date numerous vaccines have entered phase 2 and phase 3 programs but no commercially viable vaccine has been developed. Trials so far have shown that modification of the severity of acquisition illnesses, and a limited impact on the frequency and severity of recurrences is possible with some sub-unit glycoprotein vaccines<sup>54</sup> but a clinically useful effect in large-scale studies has not been demonstrated even when combined with potent immunogens.

Ultimately, a vaccine is the only practical measure to control disease and the spread of infection. The morbidity, mortality and economic impact of genital HSV are significant. Presently, prevention or amelioration of disease with or without partial protection against infection may be achievable with the vaccine,

**Table 28.10:** Types of HSV Vaccines

No. vaccine type	Status
1. Inactivated virion-derived vaccines (prepared from HSV infected cell cultures and contain both viral and cellular material).	Effective in experimental models but clinical trials have shown that they are not effective in humans.
2. Adjuvanted sub-unit vaccines (these vaccines consist of HSV proteins combined with adjuvants).	Recent trials of recombinant glycoprotein (gB2 +/- gD2) vaccines have shown limited success in phase II and failure in a large phase III study. <sup>54</sup> Failure of the 7000 patients Herpevac study of a subunit vaccine in women has recently been reported. <sup>218</sup>
3. Vectored vaccines (consist of an avirulent replication component viral or bacterial vector that has been engineered to express one or two HSV genes. Numerous vectors have been used to express HSV genes including vaccinia virus, adenovirus, varicella zoster virus and salmonella. Upon immunization the vector replicates producing the HSV gene products inducing immune response against HSV proteins).	Immunogenic and effective in animals.
4. Replication limited line viral vaccines (these vaccines are cycle without producing infectious progeny. Upon immunization, the vaccine virus infects cells and produces an aborted infection which induces immune responses).	Phase I clinical testing of one such vaccine (gH deleted) showed that vaccine is genetically engineered mutants that undergo a single replication—immunogenic. Phase II trials show only limited success to date <sup>219</sup>
5. Genetically attenuated live viral vaccines (these vaccines are replication competent HSV mutants that have had known virulence genes deleted so that they are incapable of causing disease).	Effective in animals. Human studies on going. Safety not confirmed.
6. Nucleic acid vaccines (these vaccines are based on the principle that injection of DNA encoding an immunogenic protein can induce the host to produce humoral and cellular immune responses directed against the encoded protein).	Effective in experimental models.



but it is difficult to know whether a partially protective vaccine will have a favorable impact on the ongoing epidemic of genital herpes. Thus, it is still not clear how a vaccine should be used and whether its use will be cost-effective.<sup>220</sup>

## Prevention

Two strategies can be adopted for prevention of HSV-2 transmission: (i) Interventions that will decrease viral shedding by infected persons, thereby decreasing the chance of exposure of uninfected individuals to the virus. (ii) Interventions that will render uninfected persons less susceptible to infection by the virus. Following measures can be helpful for prevention of HSV transmission:

- **Selective abstinence**<sup>221</sup>: Some patients may find this acceptable in high risk situations (e.g., third trimester of pregnancy). All patients should be advised to avoid sexual contact with unexposed partners during prodromes, lesional episodes, and in the first few days after a recurrence—this will require a degree of knowledge on the patient's part of the various manifestations of the condition as well as an appreciation of sub-clinical shedding and occasional atypical features.
- **Limiting number of sexual partners**: Levels of HSV2 in the population are correlated to sexual risk taking behavior. This may reduce the risk of acquiring genital herpes.
- **Avoiding partners who have a history of genital herpes**<sup>173,222</sup>: This does not help in prevention, as 80–90% of HSV-2 seropositive individuals have no signs or symptoms, yet they can transmit the virus to susceptible partners.
- **Consistent and correct condom use**: This may be the best practical approach to minimize the risk of acquiring genital herpes. Male latex condoms are effective at limiting acquisitions in both males and females. Consistent use is difficult to achieve but effects of protection in studies are visible even with inconsistent use. Condom usage on more than one in four occasions of sexual contact prevented 50% of HSV transmissions in a post hoc analysis of the various Chiron vaccine studies. Patients should be aware that condoms are not fully protective and that infectious virus can be shed from areas not protected or covered by barriers. There is no data for the effectiveness of the female condom.
- **Vaginal and rectal microbicides**<sup>223</sup>: This experimental approach is based on the theory that the virus can be inactivated at the portal of entry. One large study with tenofovir principally designed to look for an effect upon HIV transmission found a 50% reduction in HSV acquisitions.
- **Disclosure**: Sharing a genital HSV diagnosis with an unexposed partner is associated with a decreased risk of transmission per episode of sexual contact. The mechanism of this effect is presumably through better compliance with selective abstinence, and more consistent use of condoms. Many, possibly most patients, do not follow this advice to disclose their diagnosis—but for medicolegal purposes patients should be advised to consider this option.

- **Antiviral therapy**: This has been discussed above.
- **Vaccines**: As discussed above.

## Summary

Genital herpes is a disease of major public health importance. The last four decades have seen the emergence of HSV as the predominant cause of genital ulcer disease worldwide. The major morbidity of genital herpes is its propensity to recur frequently, its chronicity and its impact on the patient's psychosocial health. Many patients with genital herpes are unaware of their infection. When clinically apparent, clinicians need to be aware of the constellation of problems that can occur for patients and the need for careful counseling and support to manage the stigma and concern that most patients will suffer. Studies have shown the efficacy and safety of antiviral agents in controlling the symptoms of both acute and recurrent disease and in reducing serious complications particularly neonatal transmission. Concerns regarding onward transmission in relationships are common and judicious use of antiviral therapy along with patient counseling can minimize this risk. The epidemiological interactions and synergy between HSV-2 and HIV have drawn much interest in the last decade and the role of HSV-2 in fuelling the HIV epidemic has been clearly elucidated in recent studies.

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# Anogenital Human Papillomavirus Infection: Natural History, Epidemiology, and Vaccination

David Rowen • Paul Fox • Peter Goon

# 29

## Introduction

The viral etiology for the development of human skin warts was proposed in the early 20th century, and viral particles were seen on electron microscopy of wart samples in the late 1960s.<sup>1,2</sup> In 1980, Gissman and zur Hausen, isolated and characterized Human Papillomavirus (HPV) type 6 from a genital wart, thus defining one of the two main HPV types responsible for the development of anogenital warts.<sup>3</sup> Subsequently, zur Hausen postulated the link between HPV and cervical cancer in 1976 and went on to identify HPV 16 and then 18 in cervical cancers in 1983–84. Progress in HPV research has been hampered by the inability to culture the virus *in vitro*, and the absence of satisfactory animal models. Major advances in molecular, biological techniques such as DNA amplification and splicing, have, in part, circumvented some of these difficulties. These advances, together with improved understanding of the epidemiology of papillomavirus infection in respect to cervical and other lower genital tract malignancy have proven to be a major impetus to HPV research.

## Viral Structure

HPV is an unenveloped DNA virus about 55 nm in diameter and consists of approximately 8000 base pairs. It exists in three forms: form I, in which the DNA strands are covalently closed, forming superhelical twists that characterize the infectious particle; form II, which is characteristic of the replicating virus, is an open circle of DNA whereas form III is linearized following single-cut restriction endonuclease treatment. More than a hundred types of papillomavirus have now been characterized, of which approximately 40 types are known to infect the lower genital tract (Table 29.1).<sup>4,5</sup> Typing is based upon DNA homology in the L1 sequence in which more than a 10% difference in sequence defines a new type.<sup>4–6</sup>

## Viral Subtypes and Natural History of Disease

The HPV types which infect the oral and anogenital regions belong to the subdivision of HPV termed the alpha-papillomaviruses.<sup>7</sup>

HPV 16 is responsible for the majority of cervical and anal neoplasms, with closely related types accounting for much of the remainder. A significant proportion of vulval cancers can be ascribed to HPV16 whereas the role of HPV in the pathogenesis of penile cancer is less well-defined. It can be difficult to determine whether a viral type found within a neoplasm is the causative agent or not. Within such a tissue there may be small areas infected with different viral types which will also be detected by PCR testing. The best quality data is that for cervical disease, but even here doubts remain as to whether some of the uncommon HPV types play any significant role in carcinogenesis. The technique

**Table 29.1:** Genital and Related Lesions Associated with Human Papillomavirus

Lesions	Predominant HPV types
Condyloma acuminata	6, 11.
Buschke–Löwenstein tumor	6, 11
Recurrent respiratory papillomatosis	6, 11
Carcinoma of head, neck, lung	16, 18, 30
Oral papilloma	6, 7, 11, 16, 32 (also 72, 73 in HIV patients)
Carcinoma of cervix	16 (55%), 18 (16%) global averages (WHO data) <sup>10</sup> Predominant minor types: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66
CIN 1	Compared with cervical cancer prevalence of 16/18 is halved and prevalence of minor types is higher (WHO data)
CIN 2/3	16 (~ 42%), 18 (~ 7%), 31 (~ 7%), 58 (~ 8%) (WHO data).
Carcinoma of penis	16 (59% +) <sup>11</sup> Predominant minor types: 18, 35, 45.
Carcinoma of anus	16 (87%), 18 (7%), 33 (6%), 31 (1%) <sup>12</sup>
Other types occasionally associated with malignancy	40, 42–44, 53, 54, 59, 61, 68, 70, 72, 73, 81, 82 <sup>13</sup>

of laser capture micro-dissection allows extremely small areas of tissue to be sampled and analyzed, and should make it possible, in the future, to clarify some of unknowns with regard to the viral etiology of neoplasia, especially if combined with assays for HPV E6/E7 messenger RNA. A study by Insinga et al.<sup>9</sup> determined the rate of progression to cervical intraepithelial neoplasia (CIN) 1 following infection with HPV 16 and 18.<sup>8</sup> The annual progression rate was 8.3%. For CIN 2 and CIN 3, the annual incidence rate was 5.8% and 3.5%, respectively.

The encoded proteins may be divided into early (E1-7) and late (L1-2) gene products. The late gene products, L1 and L2, are structural capsid proteins, of which L1 protein makes up approximately 80% of the viral capsid, while the exact structural role of the minor capsid protein L2 has not been determined.

HPV can persist subclinically in basal epithelial cells by inducing a low rate of stable replication in infected cells through the E1 and E2 proteins. E1 is a helicase which binds to and interacts with host DNA, and E2 is involved in recruitment of E1 to the key target region. E2 also has a role in repressing transcription. In clinically evident lesions HPV has caused cells to enter into runaway or vegetative replication and the E6 and E7 proteins are crucial to this process. What factors determine whether replication is stable or becomes vegetative is unclear. E6 activates telomerase and thereby promotes continued cell proliferation, and inhibits apoptosis, while E7 inactivates the tumor suppressor gene pRb, allowing cells to enter the S phase, which is normally inhibited once cells have left the basal layer. In high-risk or oncogenic types of HPV the E6 protein has additional functions, notably the degradation of the apoptotic protein p53, and in conjunction with E7 blocks other growth arrest signals, resulting in immortalized cells. The degradation of pRb by E7 and of p53 by E6 is dependent on the human proteasome enzyme. The immortalized cells over a long period of time can thus acquire gene mutations which can give them the ability to penetrate the basement membrane and to grow within other tissues. Oncogenic HPV frequently becomes integrated into host DNA at widely variable locations, but this is not a pre-requisite for carcinogenesis.

## Immunopathology

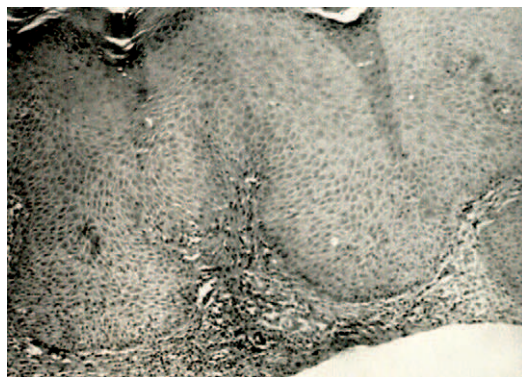
Papillomaviruses are able to bind *in vitro* in a saturable fashion to a range of epithelial cell lines. Pre-treatment of cells with trypsin reduces the ability to bind virus, suggesting that the receptor for HPV is a cell-bound protein. Studies have demonstrated α6 integrin to be a receptor molecule for both HPV 6 and 16.<sup>14,15</sup> *In vivo*, the infective process follows microtrauma to the upper layers of genital skin or mucosa that facilitates entry of the virus to deeper layers where immature keratinocytes reside. It is infection of basal keratinocytes that may result in the development of warts and/or precursor lesions of squamous cell carcinomas. Spontaneous regression of warts has been reported. In a study by Coleman et al. regression was seen in 11% of patients.<sup>16</sup> This phenomenon was associated with increased numbers of CD4+

lymphocytes both within the wart stroma and at the surface epithelium. No increase in Langerhans cell numbers was found although there was induction of HLA-DR and ICAM-1 on keratinocytes in regressing warts. Given the immune events observed in spontaneously regressing warts and the observation that individuals with inherited immune deficiencies affecting T cell responses are more prone to HPV infection, it would appear that CMI responses are essential for the control of papillomavirus infection. The reasons why, even in immunocompetent subjects, there are poor CMI responses are not well-understood. However, antigen processing via professional antigen presenting cells, that is, dendritic cells and macrophages, does not appear to be efficient. This may in part be explained by the fact that the virus is not cytolytic nor does it not have a blood-borne stage. That humoral immunity has an important role to play is demonstrated by the efficacy of prophylactic vaccines (*vide infra*), but curiously, disorders of humoral immunity have not been associated with increased susceptibility to HPV-induced lesions.<sup>17</sup> A recent study demonstrated that wart-derived chemokines attracted FOXP3+ regulatory T cells in large genital warts leading to immune unresponsiveness.<sup>18</sup>

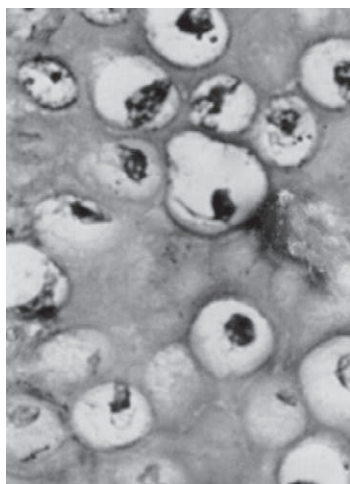
Immune evasion by HPV is achieved through several means. First, HPV is a non-cytolytic virus, and infectious particles are only produced in the upper epithelial layers at the end of the cell's lifespan and viral protein expression and replication is tightly bound to the maturation of the cell. The viral early proteins expressed in the lower epithelial layers are thought to be expressed at levels lower than those necessary for efficient triggering of the host immune response. Secondly, HPV can actively interfere with the host immune response through several of its early proteins, especially those of the high-risk HPVs. E5 interferes with HLA class II maturation and presentation,<sup>19</sup> E6 and E7 can interfere with E-cadherin expression and Langerhans cell density and can perturb function of Interferon Response Factor 3.<sup>20</sup> Therefore, there are multiple pathways by which HPV (especially HR-HPV) can evade the immune response.

## Histopathology

Histopathological features of condyloma acuminatum include slightly thickened stratum corneum, papillomatosis, and acanthosis of stratum malpighii, and thickening and elongation of the rete ridges (Fig. 29.1). There is a fibrovascular core. Other clinical variants (papular and macular) have the same features with less pronounced branching. The most characteristic feature for the diagnosis is the presence of epithelial cells with distinct perinuclear vacuolization. Such cells are known as "koilocytes" (Fig. 29.2). The vacuoles in koilocytes are sharply demarcated from the peripheral rim of condensed cytoplasm. The nucleus is hyperchromatic and large. It is important to remember that vacuolization is a normal feature in upper portion of mucosa, therefore, it is considered pathognomonic only if it extends to the deeper layers of stratum malpighii.



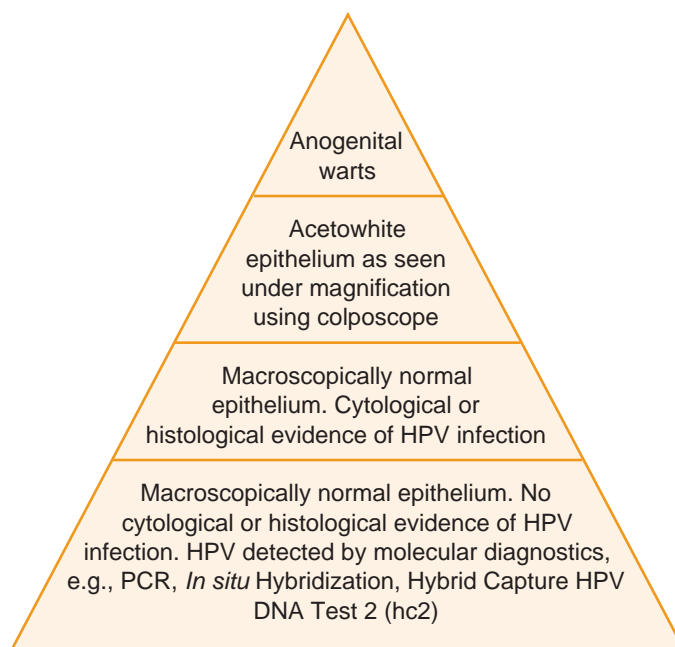
**Fig. 29.1:** Histology of genital wart—slightly thickened stratum corneum, papillomatosis and acanthosis of stratum malpighii, and thickening of rete ridges.



**Fig. 29.2:** Koilocytosis.

## Epidemiology

Anogenital warts are the most common manifestations of sexually transmissible HPV infection, and prevalence peaks during the second and third decades of life, in keeping with all other sexually acquired diseases. Reported prevalence rates of genital warts vary between 0.6% and 13% depending on the population studied.<sup>21</sup> Twenty year trends in the incidence and prevalence of diagnosed genital warts in Canada showed that the incidence reached (149.9/100,000 in men and 170.8/100,000 in women) in 1992 and has further increased in recent times.<sup>22</sup> Prevalence rates for HPV infection are, however, considerably greater. Conservative estimates suggest a two-fold increase in HPV 6 and 11 detection rates over that for the detection of warts, whereas Kataoka et al. reported a three-fold increase in detection rates of HPV using PCR technology compared with Dot blot and Southern blot analyses.<sup>23–25</sup> Genital warts as a manifestation of papillomavirus infection represent the tip of the iceberg (Fig 29.3) of HPV infection. Within the spectrum of subclinical infection there are several distinct entities, namely



**Fig. 29.3:** Manifestations of HPV infection.

acetowhite epithelium, macroscopically normal epithelium, but with cytological or histological evidence of HPV infection, such as koilocytosis, and finally macro- and microscopically normal epithelium in which HPV has been detected by such means as *in situ* hybridization or DNA amplification by PCR.

The infectivity of patients with warts is well-documented. Up to two-thirds of their sexual partners will, within six months, develop warts.<sup>26</sup> Given the high prevalence of sub-clinical infection, it is likely that transmission from sub-clinical lesions is common.<sup>17</sup> Occasionally, anogenital warts may be caused by papillomavirus types associated with hand warts, namely types 2 and 4.<sup>27</sup> Genital HPV is less common in circumcised men, and cervical cancer risk is reduced among female sex partners of circumcised men.<sup>28</sup>

Around 70% of genital HPV infections clear within 1 year and 90% within two years, leaving a small proportion of patients with more long-standing infection which might persist for decades. HPV 16 takes longer to be cleared by the immune system than other types, having a median duration of 8 months, compared to 3–4 months for HPV 6, 11, and 18. It has not been determined whether the virus can persist indefinitely undergoing stable replication without producing any further clinical warts or not, but in practical terms such questions are irrelevant for most patients.

## Laboratory Diagnosis

In majority of HPV-infected individuals, no visible lesions are apparent. In the absence of clinical manifestations, genital HPV infection can be difficult to detect. Diagnostic methods used to diagnose other viral infections (e.g., growing virus in cell culture) cannot be successfully applied to HPV. Therefore,



clinical diagnosis and cytologic alterations remain the most frequently applied diagnostic criteria for genital HPV.<sup>29</sup> Biopsy for histological confirmation may be required if there is concern about the development of intraepithelial neoplasia, for example, vulval intra-epithelial neoplasia, anal intra-epithelial neoplasia. Some authorities recommend biopsy if the lesion is of the macular or papular variety and the patient is over 35 years of age.<sup>30</sup> There is no evidence to support the use of HPV typing of anogenital warts; it does not add any information that is clinically useful. The role of cytology by Pap smear examination for features of koilocytosis and dyskaryosis and histology in the diagnosis of cervical neoplasia is well-established. Koilocytic cells are considered as part of the spectrum of the lowest grade of CIN 1. The sensitivity of Pap smear is poor, though specificity is very high (approximately 90%). To increase its sensitivity FDA has approved Hybrid capture HPV DNA test 2(HC2) to be performed in conjunction with Pap smear.<sup>31</sup> The HC2 test can detect as little as 1 pg of HPV DNA/ml; its sensitivity and specificity are almost comparable with PCR-based detection methods. The advantages of the HC2 test are the relatively simple handling and good reproducibility of results, which make this test the best standardized HPV detection method. While the exact HPV type cannot be identified “low-risk” (6, 11, 42, 43, 44) and “high-risk” (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) HPV genotype groups (HR HPV and LR HPV) are detected.

Revised recommendations of American College of Obstetricians and Gynecologists (ACOG) for Pap smears.<sup>32</sup>

- Women from ages 21 to 30 be screened every two years instead of annually, using either the standard Pap or liquid-based cytology.
- Women aged 30 and older who have had three consecutive negative cervical cytology test results may be screened once every three years with either the Pap or liquid-based cytology.
- Women with certain risk factors may need more frequent screening, including those who have HIV, are immunosuppressed, were exposed to diethylstilbestrol (DES) *in utero*, and have been treated for CIN 2 or 3, or cervical cancer.

Serology has been used as a marker of infection, but its clinical relevance is limited. The appearance of antibody lags behind the detection of papillomavirus DNA, typically taking 6–12 months to develop, so the antibody response might only be detected after clearance of the virus. Many people with persistent infection do not have detectable antibodies, but this could be due to poor assay sensitivity. How long serological markers can persist is not well-documented. Serology has little value in the diagnosis because of its low sensitivity and specificity. One serological parameter that may be useful for following the course of HPV disease is seroreactivity to the E6 and E7 portions of oncogenic HPV types that are capable of transforming cells in culture. Dereglulation of these genes appears to play a key role in the malignant conversion of cervical cancer precursor cells.

Various methods used for DNA detection include Southern blot, Dot blot, *in situ* hybridization, and polymerase chain reaction. Southern blot hybridization is considered as the “gold

standard” for the detection of HPV DNA because of its high sensitivity and specificity; however, it is too cumbersome and slow for routine use.<sup>23</sup> It is implied only for research purposes and for quality control.

## Vaccines

There are currently two prophylactic virus-like particle (VLP) vaccines available, Gardasil (Sanofi-Pasteur MSD), a quadrivalent vaccine containing VLPs for 6, 11, 16, and 18; and Cervarix (GSK), a bivalent vaccine containing the VLPs for 16 and 18. In 1999, it was reported that the L1 capsid protein naturally refolded into a three-dimensional conformational structure, was for all intents and purposes, a perfect copy of the exterior of the natural virus particle.<sup>33</sup> This seminal discovery allowed the subsequent development of VLP vaccines. Passive transfer of serum into naïve animals from previously VLP-vaccinated animals showed that animals could be completely protected from infection with live virus.

The outstanding feature of these 2 vaccines has been the almost 100% protection from clinical disease such as high-grade CIN 2/3, which are accepted as the precursor lesions of malignant transformation. Furthermore, it has been shown that the quadrivalent vaccine is fully protective against clinical disease from genital warts caused by types 6 and 11. The protection against clinical end-points of disease has been shown to extend until the present day (at time of printing). Both vaccines will protect against approximately 70% of cervical cancer cases. Women already infected with the subtypes contained in the vaccines will not have this protection and will still be at risk of infection from non-vaccine subtypes in the future.<sup>34</sup> The vaccines have been shown to provide a degree of cross protection against subtypes not included in the vaccines such as types 45 and 31.<sup>35</sup>

The mode of action of these vaccines is thought to be the induction and production of anti-L1 antibodies. The VLPs are potent immunogens (enhanced by adjuvant in the vaccines) and given via the intramuscular route, which ensures rapid dissemination of the antigens to the lymph nodes. This results in high levels of neutralizing antibodies, which are able to bind to virus and prevent entry and infection of cells. These levels of antibodies are usually 2–3 logs higher than that seen in natural infection with the virus.<sup>36</sup> There is poor correlation between antibody levels and efficacy, and those with very low or even undetectable antibody levels might have protective immunity. HPV almost certainly requires breaks in the epithelium down to the level of the basement membrane to establish an infection. When such breaks occur they are rapidly filled with serum containing neutralizing antibody. HPV antibody appears to be able to prevent such infections at very low concentrations. Mathematical modeling of the duration of antibody responses based on current knowledge of virology, vaccinology and immunology predicts that benefit of vaccination is likely to be life-long, with a reduction of natural diseases in 76%.<sup>37</sup>

The current vaccines are expected to confer a degree of protection against all HPV-related cancers, such as other

anogenital cancers (i.e., anal, vulval, vaginal, penile, etc) and subsets of head and neck cancers, in which the dominant subtypes are HPV 16 and 18. The quadrivalent vaccine will additionally protect against the development of genital warts and recurrent respiratory papillomatosis. Most countries which have been able to afford the vaccine have so far opted to vaccinate only young women, which has had the impact of reducing disease in young men also. Ideally, young men, especially men who have sex with men, who will not benefit from this type of vaccination strategy, but who carry a significant risk of infection, should also be vaccinated. Although health strategists might not consider this to be “cost effective” in terms of money saved, men could be protected against both warts and HPV-related cancers, and their vaccination would also benefit herd immunity.

Recent data from Melbourne, Australia, where the quadrivalent vaccine was introduced for young women in April 2007, has shown a halving in diagnoses of genital warts in women under 28 years of age, and a 17% reduction in diagnoses in heterosexual men.<sup>38</sup>

Although the vaccines are prophylactic and therefore need to be targeted pre-sexual debut to prevent infection, there is evidence that there is clinical benefit for the vaccination of young women who are already sexually active.<sup>39</sup> A young woman already infected with one subtype should derive protection from the remaining subtypes in the vaccines. Currently there are attempts to produce the next generation of prophylactic vaccines based on the L2 protein, which it is hoped might produce near “universal” coverage of subtypes.<sup>36</sup>

## Conclusion

There have been considerable advances in recent years in the understanding of the natural history of HPV infection, and much of this has been a consequence of the vaccine development program. There remain many unanswered questions such as the exact nature of the complex virus-host interaction which confers viral oncogenicity, the understanding of which might lead to new cancer treatments; how long HPV might remain latent and inactive within the epithelium, and whether this matters clinically; whether different types of HPV might have a synergistic role in the development of cancer; and what types of HPV are truly oncogenic in different clinical contexts? As we move forward into a world in which more and more people are vaccinated against a small number of viral types, the need to answer to questions such as these will become increasingly necessary.

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# Anogenital Warts, Intraepithelial Neoplasia, and their Clinical Management

Paul Fox • David Rowen

# 30

## Introduction

Anogenital warts have been recognized as a disease entity for many centuries. They were certainly recognized by early Greek and Roman physicians, such as Hippocrates and Galen. The term condyloma is derived from ancient Greek, meaning “a round swelling adjacent to the anus.” The addition of the suffix *acuminata* is a relatively new feature, appearing towards the end of the 19th century. The perception that anal warts were a manifestation of a homosexual lifestyle is evident from writings of the first century; writings from the sixth century suggest that cautery was used as a treatment and that surgeons had little sympathy for their patients with anal warts.<sup>1</sup> The spectrum of HPV related disease is protean.

## Clinical Features

Anogenital warts are often multifocal. The most common sites, in the uncircumcised male, are the glans, the inner aspect of the prepuce (Fig. 30.1) and the frenulum.<sup>2</sup> In circumcised males, the shaft is also commonly affected. In females, warts are found commonly affecting the labia minora and majora, introitus (Fig. 30.2), the posterior fourchette extending onto the perineum, and in the perianal region.<sup>3</sup> These locations in both men and women tend to be the sites most prone to microtrauma during sexual intercourse, which facilitates viral access to the basal layer.

In men the urinary meatus is affected in up to 25% of cases, whereas in women, this site is affected only in 4–8%. Warts occur less commonly inside the vagina and can sometimes be detected on the cervix on speculum examination (Fig. 30.3). The morphology and pigmentation of warts is, in part, determined by their anatomical location. Pigmented warts (Fig. 30.4) are not uncommon in hairy areas including the labia majora, penile shaft and perianal area, and pigmentation at these sites should not cause alarm.

Warts may be broadly divided into three major morphological groups: acuminate warts, which are found on mucosal surfaces and are characterized by being formed around vascular, finger-like

projections (Fig. 30.5). They usually have an irregular surface, which may give the appearance of fissuring. Individual lesions may coalesce to form larger lesions, which are not infrequently seen in pregnancy and in immunodeficient states. Bleeding can occur following minor trauma because of the vascularity and this may be the presenting complaint.

Another type is the flat or macular wart, which can be difficult to distinguish from low grade intraepithelial neoplasia (*vide infra*) and other skin conditions. A traditional way of distinguishing HPV related lesions from other lesions is to cover then with a piece of gauze soaked in 5% acetic acid for 5 minutes. Warts



**Fig. 30.1:** Warts on the inner surface of prepuce.





**Fig. 30.2:** Warts in the vagina.



**Fig. 30.3:** Wart on the cervix.



**Fig. 30.4:** Pigmented papular warts.

and intraepithelial neoplasia will become white, the so-called acetowhite, but the specificity of the procedure is low because inflammatory lesions can also be highlighted.<sup>3</sup>

The third morphological wart type is thick, papular, highly keratinized variety which tends to occur in extramucosal locations on stratified squamous epithelium, analogous with common warts.

A rare variant is the so-called Buschke–Löwenstein giant tumor (Fig. 30.6). This HPV-6 and 11-associated lesion is characterized by downward growth into dermal structures. Although locally invasive, it does not metastasize, except in immunocompromised patients such as those with HIV infection, in whom there is a risk of transformation into squamous cell carcinoma.<sup>4</sup> Histologically



**Fig. 30.5:** Accuminate warts.



**Fig. 30.6:** Giant condyloma in a HIV positive patient (Buschke–Löwenstein tumor). *Courtesy: DG Saple, Mumbai, India.*

the lesion forms a complex pattern of acanthosis, koilocytic changes as well as foci of markedly atypical squamous cells.

The psychological impact of developing anogenital warts should not be underestimated. Many patients will be distressed, experience relationship difficulties due to concern about infidelity of their partner, and express feelings of low self-esteem.<sup>5</sup> Some patients, especially women, will be concerned with regard to malignant transformation of anogenital warts and whether the warts will affect fertility.

The complications of genital HPV during pregnancy include rapidly enlarging and spreading warts and obstruction of the birth canal when large condylomatous lesions fill the vaginal outlet. Neonatal laryngeal or respiratory papillomatosis can occur when HPV is vertically transmitted from mother to the newborn during vaginal delivery.

## Differential Diagnosis

The differential diagnosis of genital warts include pearly penile papules, vulvar papillomatosis, skin tags, molluscum contagiosum, seborrheic keratosis, bowenoid papulosis, and squamous cell carcinoma of penis or vulva.<sup>6</sup>

Recurrent respiratory papillomatosis is rare, affecting only 4 per 100,000 live births, but is extremely distressing and expensive to manage.<sup>7</sup> In order to prevent this, some clinicians advise women with clinically evident genital warts to have delivery by caesarian section, but this is far from common practice.<sup>8</sup> There have been rare instances of children being affected despite caesarean section, presumably as a result of transplacental infection.<sup>9</sup> The papillomas typically occur in the upper respiratory tract, especially the soft palate, epiglottis, and the bronchial spurs, but ciliated epithelium anywhere within the respiratory tract can potentially be infected. Respiratory obstruction can supervene, and regular surgical clearance is often necessary. Malignant transformation occurs in 3–7% of cases typically in association with HPV-11. The condition can also develop in adulthood, presumed usually to be a rare consequence of sexual transmission, but it has also been known to affect surgeons performing electrosurgery on warts with inadequate smoke extraction.

## Management

The aims of treatment should be carefully explained to patients, as also the reason for treating the warts.<sup>10</sup> The major reason for treatment is for cosmetic purposes. Treatment may also reduce infectivity, although there is no overwhelming evidence to support this contention. It should be noted that HPV-6 and 11, the usual cause of anogenital warts, have little oncogenic potential and patients can be reassured accordingly. Patients should also be advised concerning latency of papillomavirus; the partner from whom they acquired the virus may not be their current one. Patients presenting with warts should routinely be screened for other sexually transmissible infections.<sup>11</sup> Patients with warts at the anal margin should have the anal canal visualized using a proctoscope, as a high proportion will have additional warts at this site. This might reasonably be deferred until the external warts have been cleared, unless the patient has intra-anal discomfort suggestive of the presence of warts. There is always a possibility that clearance of external warts might lead to spontaneous resolution of the internal warts through the development of effective immunity. Patients with perianal warts are frequently concerned that they may be thought to have engaged in receptive anal sexual intercourse. Although such warts may result from virus transmitted by this means, it is much more likely that perianal infection results from spread of infection from adjacent sites. Warts at the anal margin can sometimes be a consequence of scratching in a patient with perianal warts, but for true intra-anal warts there is a strong association with receptive anal intercourse.

The treatment of anogenital warts is determined by the size, and anatomical site of the warts, whether the warts are keratinized or fleshy. No specific treatment is appropriate for all patients. One

should always consider the option of not treating the warts, as it has been reported that spontaneous resolution of warts may take place. Coleman et al. reporting a 50% spontaneous regression in wart size in a fifth of patients over a 4-week period.<sup>12</sup> Controlled treatment studies have invariably shown that a significant portion of warts will also be cleared in the placebo arm. Warts may grow rapidly in pregnancy, but can regress with similar rapidity following delivery. The majority of the treatment modalities aim at wart clearance, the underlying HPV infection is not addressed. Hence, recurrence following apparently successful treatment is not uncommon. Reported recurrence rates range from 0–91%, dependent on treatment modality.<sup>13</sup> All treatment modalities will, to some extent, cause local skin reactions, e.g., erythema, ulceration, and localized soreness, and patients should be advised accordingly.

## PODOPHYLLIN

Kaplan first described the use of podophyllin in 1942.<sup>14</sup> The source of the drug is the root of *podophyllum emodii* or *peltatum*. The crude extract is usually suspended in compound tincture of benzoin or in alcohol. It can also be mixed with white soft paraffin and be used as an ointment. The active ingredient in this crude extract is podophyllotoxin. Unfortunately, the amount of active material in any extract varies considerably from batch to batch, as does the amount of lignans such as quercetin.<sup>15</sup> It is these lignans which are responsible for most of the side effects of the drug. The suspension has a relatively short shelf life, although probably stable up to 3 months without undue loss of potency. A commonly followed regimen is the application of podophyllin, 25% in tincture benzoin, once or twice weekly, the suspension being washed off after 4–6 hours. Several studies have shown that more dilute podophyllin in an alcoholic vehicle, applied more frequently, is as effective as 25% podophyllin or commercially available podophyllotoxin. Highly keratinized warts do not appear to respond well to treatment with this drug, although no randomized, controlled trials have been carried out to prove this. The most common side effect of the drug is localized soreness and ulceration. Washing the podophyllin off, 4–6 hours after application, may minimize the risk of this. Podophyllin contains neurotoxins, which can cause nerve damage, and there have been rare instances of coma and death. This is seen only when a considerable amount of the drug has been absorbed through the mucosa, but patients should never self apply this treatment and it should not be applied to large areas. The drug is also potentially mutagenic and therefore should not be used in pregnancy due to the theoretical risk of teratogenicity.

## PODOPHYLLOTOXIN

The active agent of podophyllin has been purified and is available commercially both in a liquid form and as a cream. It is considerably more expensive than podophyllin, but is suitable for home treatment, therefore negating the necessity for the patient to attend clinics for treatment. It contains no neurotoxins and is an extremely safe treatment except in pregnancy because of the



potential risk of teratogenicity. Side effects of the drug are less commonly observed than with podophyllin. It is applied twice daily for 3 days each week either as a lotion or a cream, more frequent application being associated with increased frequency and severity of side effects. Several studies have demonstrated superiority over podophyllin suspension for the clearing of warts.<sup>16</sup> Apart from its low cost, podophyllin has no advantage over podophyllotoxin. Once cost benefit versus risk ratio is considered, it becomes clear that self treatment with podophyllotoxin is more efficacious than podophyllin.<sup>17</sup> Meta-analysis of podophyllotoxin studies has shown that it produces a complete clearance after 4 weeks in 49% of patients, and an overall sustained clearance at 12 weeks in 35%.<sup>18</sup>

### MONOCHLOROACETIC AND TRICHLOROACETIC ACID

The use of caustic agents such as mono- or trichloroacetic acid is of value, especially in the treatment of flat warts. Great care is required when applying to prevent burning the adjacent normal skin. Absence of systemic toxicity means that both agents can safely be used in pregnancy. Their use at the meatus is best avoided, to prevent meatal stenosis. The acid can be applied by touching the warts with an orange stick that has been dipped in the acid. Application with a swab is potentially dangerous as the amount of acid may be excessive and damage to adjacent skin is a possibility. The treated area rapidly goes white due to precipitation of protein within the wart. Patients often experience a warm sensation soon after the application. Frank discomfort is uncommon unless excessive amount of acid has been applied. Ideally the warts should be treated at weekly intervals.

### CRYOTHERAPY

The value of cryotherapy as a treatment modality is its versatility. It can be used on all types of warts, is not restricted to use at specific anatomical sites, and is safe in pregnancy. Some immediate discomfort at the site of treatment may limit its use in those with a low pain threshold. Topical local anesthetics can be applied, although these are usually considered to be unnecessary. When the cost of clinical time is factored, cryotherapy shares with mono- and trichloroacetic acid in being the least cost effective treatments because weekly treatments are required.<sup>19</sup> Furthermore, the cost of the equipment can be prohibitive in resource poor settings. The liquid nitrogen can be applied in two ways: either with a liquid nitrogen spray, or by dipping a Dacron swab into liquid nitrogen and applying this to the wart. The minimum duration of application should be that required to produce a frozen halo around the wart. The longer that the freezing is sustained the higher the likelihood of clearance, but freezing for prolonged period involves the risk of significant pain and blistering. One way of freezing for longer periods while reducing the pain experienced is to use a double freeze-thaw cycle. Another way when using the nitrogen jet is to use an interrupted jet with only enough freezing to maintain the frozen halo. In this way the tissue can be held frozen for up to 30 seconds with minimal discomfort. Cryoprobes, using either carbon dioxide or nitrous

oxide as the cryogen, are also effective; however, the equipment required can be costly. There have been concerns with regard to accumulation of nitrous oxide in the immediate environment especially when ventilation is inadequate.<sup>20</sup> There are at least three phases involved in cryodestruction, namely: the physical, vascular, and immunological. It is probably the immunological phase that is responsible for the lower recurrence rate observed following treatment with cryotherapy than with some other modalities.

### 5-FLUOROURACIL

This anti-metabolite has in the past been used topically for the treatment of warts. Side effects, namely irritation and ulceration limit its use. Furthermore, it cannot be used in pregnancy. Few trials have examined the efficacy of this substance. Guidelines do not recommend its use for the treatment of genital warts. However, a Cochrane review concluded that, 5-FU was superior both to placebo and podophyllin when the outcome considered was cure alone.<sup>21</sup>

### IMIQIMOD

This modality has a different mode of action to other wart treatments.<sup>22</sup> It is an immune response modulator which takes an average of 9 weeks to clear the warts.<sup>23</sup> The main action of imiquimod is on toll like receptors (TLR-7 and TLR-8). This activates nuclear factor kappa B (NF- $\kappa$ B) which in turn induces transcription of genes for cytokines, interferons (IFN- $\alpha$ ), tumor necrosis factor (TNF- $\alpha$ ), interleukins (IL)-2,6,8, and 12, granulocyte colony stimulating factor and granulocyte macrophage colony stimulating factor. In addition, it also releases chemokines and other inflammatory mediators. As a result of this, there is activation of cytokine producing dendritic cells and antigen presenting Langerhans cells.<sup>24</sup>

It is more effective when applied within skin folds, i.e., underneath the foreskin, in the vulva and perianally, presumably because the occlusive effect aids absorption. It is therefore most effective in women, with an end of treatment clearance of 72%. In trials where a high proportion of men were circumcised clearance falls to 37%, while in a study looking only at uncircumcised men clearance was 62%.<sup>19,25</sup> A study in which male patients were randomized to treatment with either imiquimod or cryotherapy showed that cryotherapy was slightly less effective after 3 months of treatment, and that the recurrence rate was less with imiquimod.<sup>26</sup> A meta-analysis has shown that daily application of imiquimod has no benefits over 3 times a week application. Therefore the current recommendation on frequency of application is 3 times a week.<sup>27</sup>

If there has been a partial response to the first 12 weeks of treatment, a further course will produce clearance in 27%, and for patients who developed recurrence the clearance rate was 58.5% on reapplication.<sup>28</sup> Recurrence rates are around 22% in the 3 months following effective treatment, but if treatment has previously been effective it will usually be effective when used again, and often in a shorter time frame. Patients should be warned to expect irritation and erythema at the site of application and sometimes in areas

infected with HPV where no cream has been applied. This is a common cause for discontinuing treatment, and it is helpful to give patients permission to discontinue therapy while soreness is present, and thereafter the dosage and frequency might need to be reduced. The drug is costly compared with other drugs if three boxes of imiquimod are used over a 12-week period, but if each sachet is made to last a week so that only one box is used, then it becomes perhaps the most cost effective treatment, especially for women and uncircumcised men. There has recently been some concern on theoretical grounds that treatment of warts may facilitate the transmission of HIV to susceptible patients.<sup>29</sup> This hypothesis is however not widely accepted. Imiquimod has been frequently associated with local and systemic adverse events, even induction of non dermatologic disorders. Rarely, erythema multiforme has been attributed to imiquimod.<sup>30</sup> A potential side effect of imiquimod is depigmentation of the skin following effective cure. This looks similar to vitiligo, which has also been observed to develop in the zone of application during treatment.

### SURGICAL EXCISION AND LASER

There are a number of different surgical treatment options including scissor excision, electrosurgery/hyfrecaction, and laser. These procedures can often be undertaken under local anesthetic unless the warts are very extensive or in a difficult location such as intravaginal or intra-anal, when a general anesthetic will be required. Data on comparative efficacy compared to other treatments are extremely scanty. The results of the few trials that have been published indicate that recurrence rates following scissor excision are lower than in patients treated with podophyllin.<sup>31</sup> This information is not all that useful in view of the fact that podophyllin has been established as the least effective of all the treatments for warts. Certain types of warts such as pedunculated warts lend themselves extremely well to the surgical approach, but this aside, surgery is generally considered to be a treatment of last resort after the failure of other treatment modalities because it is time consuming, painful, and can lead to considerable post operative morbidity. Among anal condylomata acuminata, HPV-11 was found to be associated with higher recurrence rates after surgical excision than other HPV types.<sup>32</sup>

An auto-implantation technique has been described.<sup>33</sup> Recurrence of warts following use of this technique was

significantly lower than in a comparable group treated with podophyllin. CMI responses were measured and these appear to be enhanced by this technique.

Carbon dioxide laser can be used for ablation. Cao et al. found that low dose cyclophosphamide prevented recurrence of large condylomata acuminata after laser ablation. The mechanism suggested was depletion of regulatory T cells by low dose cyclophosphamide and effective immune response.<sup>34</sup>

Flashlamp-pumped pulsed dye laser emits in the yellow orange part of the visible light spectrum at 585 nm. The application of 585-nm flashlamp-pumped pulsed dye laser (FPDL) light appears to be a safe and simple treatment option for the management of genital warts. The laser beam targets dilated capillaries in genital warts. Many patients require more than one session.<sup>35</sup>

### INTERFERONS

The use of interferons both as primary treatment and as an adjunct to other therapies post clearance has yielded disappointing results.<sup>36,37</sup> They are expensive, and side effects such as flu-like symptoms are common. Their use for treatment of warts therefore cannot be justified.

### COMBINATIONS OF TREATMENT MODALITIES

The use of combined treatments, such as cryotherapy plus topical podophyllin has lately become a popular choice of therapy. A comparative treatment study has usefully compared five different treatment modalities, podophyllin, TCA, and cryotherapy, with two combined treatment approaches, TCA and podophyllin, and finally cryotherapy and podophyllin.<sup>38</sup> This showed that TCA and podophyllin have similar efficacy and were both markedly less effective than cryotherapy. Combining TCA and podophyllin gave them comparable efficacy to cryotherapy, but adding podophyllin or podophyllotoxin to cryotherapy produced no significant additional benefit.

### NEWER/EXPERIMENTAL TREATMENT MODALITIES

Intralesional immunotherapy with antigens and vaccines unrelated with HPV has been found effective in different trials. No randomized controlled trials are available and intralesional injection is painful. A summary of published studies is given in Table 30.1.

**Table 30.1:** Summary of Published Studies on Intralesional Antigen Therapy for Anogenital Warts

Authors, Year	Antigen used	Mode of application	Total no. of patients	No. of patients completely cleared
Malison and Salkin, 1981 <sup>39</sup>	BCG	Intralesional	2	0 (0%)
Böhle et al. 2001 <sup>40</sup>	BCG	Topical	10	6 (60%)
King et al. 2005 <sup>41</sup>	Mumps, candida or trichophyton	Intralesional	21	5 (23.8%)
Metawea et al. 2005 <sup>42</sup>	BCG	Topical	25	23 (92%)
Gupta et al. 2008 <sup>43</sup>	Mycobacterium w	Intralesional	10	8 (80%)
Eassa et al. 2011 <sup>44</sup>	PPD	Intralesional	40	19 (47.5%)



## GREEN TEA CATECHINS

In 2006, 15% sinecatechins ointment was approved by US-FDA for topical treatment of genital warts. The drug is derived from leaves of green tea (*Camellia sinensis*). It consists of a mixture of catechins, their derivatives, and other components of green tea.<sup>45</sup> They have antioxidative, immunostimulatory, and antiviral properties. They inhibit pathways that are activated by HPV oncogenes. Sinecatechins specifically reduce the expression of HPV gene products E6 and E7.

Sinacatechins ointment is to be applied 3 times a day, up to 250 mg per application. A randomized trial reported 57.2% clearance in drug group vs 33.7% in vehicle group ( $p < 0.001$ ), 3.7% developed new warts, 6.5% showed recurrence during 12-week follow-up period.<sup>46</sup>

There was no significant difference in local reactions between drug and vehicle group. Like imiquimod, sinecatechins are more effective in women than men.

## PHOTODYNAMIC THERAPY

Aminolevulinic acid (ALA) photodynamic therapy (PDT) has shown good results in few trials with up to 60% clearance rates.<sup>47</sup> It has been found to attract antigen presenting cells in HPV infected epidermis and resultant effector T cell response.

## WARTS IN MORE DIFFICULT TO TREAT LOCATIONS: INTRAVAGINAL AND INTRA-ANAL

Cryotherapy and TCA are very difficult to use effectively at these sites. Podophyllin should not be used, but both podophyllotoxin and imiquimod creams can be very effective if used cautiously. Less than half a sachet of imiquimod should be used because systemic absorption can occur, which may result in transient flu-like symptoms many hours later. Patients who experience such a reaction are unlikely to have further problems if the dosage is further reduced. If these treatments fail then surgery is the only option. Cervical warts are best removed colposcopically.

## Prevention

The consistent use of condoms has been demonstrated to reduce the risk of acquiring genital warts.<sup>48</sup> The use of condoms while a patient is receiving active treatment for warts, and for 3 months post treatment, is often advised as a means of preventing transmission and to prevent recurrence. This advice is without any scientific justification. One study has shown some benefit for the index case with regard to time to clearance, but no published studies have shown unequivocal benefit for partners of the index case.<sup>49</sup> If patients are in long term relationships and they have been having unprotected intercourse, it is likely that both share the same type of papillomavirus, and the use of condoms at this stage is unlikely to prevent the development of warts in partners or have impact on recurrence rates. Condom use with regular partners has not been shown to affect the outcome of other manifestations of HPV infection.<sup>50</sup>

## Penile Intraepithelial Neoplasia (PIN), Vulval Intraepithelial Neoplasia (VIN), and Anal Intraepithelial Neoplasia (AIN)

Collectively these squamous intraepithelial lesions (SIL) can be divided into three basic types: subclinical, appearing only following the application of acetic acid; resembling flat warts; and thirdly and most distinctive, giving rise to red velvety lesions which have an eroded appearance because there is no normal epithelium. Histologically, SIL can be divided into low grade or grade 1 and high grade, grade 2 or 3 on the basis of whether the atypical layer of cells is confined to the locality of the basement membrane (grade 1), occupies the full thickness of the epidermis (grade 3) or is intermediate between the two (grade 2). Virologically low and high grade are distinct, with the majority of low grade lesions being associated with nononcogenic HPV-6 and 11, and the majority of grade 3 lesions being caused by oncogenic HPV types, predominantly HPV-16 and 18.<sup>51,52</sup> In an observational cohort of women in the placebo arm of an HPV vaccine study, HPV-6 or 11 was found in 65% of women who developed VIN 1. Only 6% had HPV-16 or 18, whereas 65% of those with VIN 2/3 had HPV-16 or 18.<sup>53,54</sup> It is likely that much low grade SIL is misidentified as warts and effectively treated using the customary treatments for warts. This hardly matters because such lesions have little or no malignant potential. High grade lesions which have been static in one location for a long time might undergo malignant change. It is difficult to determine an individual's risk of malignant transformation but age, smoking, and immune status (e.g., HIV positive, on corticosteroids or other immunosuppressants) should be taken into consideration when assessing risk. HPV related squamous carcinoma is extremely rare below the age of 50 years, whereas SILs are common. Even in HIV-positive patients, the rate of malignant conversion is unlikely to exceed 4% per annum. When SIL does undergo malignant change this typically manifests itself clinically as a thickening of part of the lesion which thus becomes more papular, in contrast to the normal macular appearances. Such lesions should be completely excised as a matter of urgency.

Treatment options are similar to those for warts, including surgical removal, TCA, cryotherapy, and imiquimod. The latter treatment has been shown to be highly efficacious for VIN in a placebo controlled study.<sup>55</sup> Therapeutic vaccines are a potential future treatment option. These aim to stimulate an immune response to the oncogenic E6/E7 proteins. A variety of candidate vaccines have been produced, and one of these has so far shown efficacy in the treatment of VIN based on preliminary results, but with severe local side effects at the injection site.<sup>56</sup> Prophylactic vaccination does not induce regression of SIL, although there remains a theoretical possibility that it might have a protective benefit in preventing the development of lesions in new areas.

The anal squamocolumnar junction is structurally very similar to that on the cervix, and there are reports that heterosexuals who have never engaged in receptive anal intercourse can develop AIN at this site, although the risk is very much greater if there

is a history of receptive anal intercourse. Cohort studies using cytology have shown that at least 5% of MSM, both HIV positive and negative, have SIL across all age cohorts, but the incidence of anal cancer is very much greater in the HIV positives, showing a steep rise over the last 10 years.<sup>57</sup> A range of treatments have been used for anal canal AIN, including imiquimod, TCA, laser, infra-red coagulation, and electrofulguration. All of these methods are used in conjunction with high resolution anoscopy, a procedure very similar to colposcopy. There are high recurrence rates with all these treatments in HIV positive individuals, but there are benefits to sustained treatment. Long-term follow-up of two clinic cohorts of HIV positive patients who have undergone treatment over several years for high grade internal AIN show an overall sustained absence of high grade lesions in 61% of patients.<sup>58,59</sup> The treatment modalities used at these two centres were imiquimod, TCA, and laser. Cytological surveillance to detect AIN is starting to be used more and more in high-risk populations, so that those with high grade disease can be aware of an increased risk of cancer. Regular digital anal examination for any lumps by the patient and/or the clinician in this group is advisable to pick up anal cancer at an early stage when simple surgical excision would usually be curative.

### Summary

Given the scale of papillomavirus infection, with either high or low risk types, it is clear that there is need for strategies, both to prevent primary infection, and to deal with established infection and its sequelae. Condom use may prevent initial infection, but once infection is established the benefits of condom use are much less certain. The wide range of treatments available is a reflection of the fact that there is no ideal treatment. There is no single treatment modality that is suitable for all patients with anogenital warts. No currently available treatments, with the exception of imiquimod, target the virus. Consequently recurrences are not uncommon. All treatments, including imiquimod, have definite failure rates with regard to both clearance and recurrence. Utilization of the new quadrivalent HPV vaccine offers great hope for the future, but the current high cost precludes its use in the developing world where it is most needed, and vaccination cannot help individuals who have already acquired HPV infection.

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# Molluscum Contagiosum

Jyoti K. Dhar

## Definition

Molluscum contagiosum (MC) is a benign proliferative skin condition lasting several months and commonly affecting children, sexually active adults, and immunocompromised individuals. Bateman, as early as 1817, assigned the condition its name based on the characteristic appearance and expressibility of a milky fluid. This expressed material was considered infectious (Handerson–Peterson or molluscum bodies) besides being responsible for transmission.<sup>1</sup>

The viral nature of MC was first hypothesized in 1905 by Julius Burg. In 1933, it was established that infection is caused by a double-stranded DNA virus of the pox family, a sole member of the genus Molluscipox virus, represented by MCV1 and MCV2.<sup>2</sup> The MCV is the largest of all animal viruses currently known and is easily visualized on light microscopy. Following the eradication of smallpox, it remains the only poxvirus to infect humans. Unlike smallpox, however, infection with MCV has not been clinically significant, except during the pre-HAART (highly active antiretroviral therapy) period of HIV disease when clinical presentation with MC is common, causing serious morbidity in HIV-infected individuals.

## Pathogenesis

The exact pathogenesis of MC is unclear and has not been completely elucidated. Immunity, both cellular and humoral, appears to play an important role in the resolution of established infection. Transmission occurring through direct skin contact with an infected individual is well-recognized. Viral inoculation is triggered by superficial damage to the epithelium. Abnormal epithelial cell proliferation of the basal layer with acanthosis follows, leading to the hyperplastic, folded epithelium. The presence of free virus cores, or viral factories, has been reported, mainly affecting all the layers of the epidermis, including the malpighian and granular cell layers.<sup>3</sup> A few studies have shown mononuclear infiltration occurring in the healing stage of the infection. It is postulated that the viral localization in the epidermal keratinocytes, the lack of inflammatory cell infiltrate seen in *in vivo* lesions, and the noticeable absence of T and NK

cells in molluscum lesions may partly explain the phenomenon of immune evasion (see below).

These skin lesions or “pocks,” as they are sometimes called, are small and can persist for months before resolving spontaneously.

In patients with impaired immunity, they have been noted to become larger and persist for longer periods.

Research into MCV has also been hindered by an inability to replicate the virus in tissue culture (which appears to be due to a defect in the expression of the genome) and the absence of useful animal models. Currently, there is no *in vitro* or animal model available for MCV, and while investigators have been able to infect human skin with molluscum contagiosum virus and graft it onto athymic mice, no continuing viral replication was noted.<sup>4</sup>

The MCV genome is a linear, double-stranded DNA molecule of 180–200 K bases; in length, a continuous strand of self-complementary DNA. Structural similarity of the MCV DNA to the vaccinia virus DNA implies a similar mechanism of replication. DNA restriction endonuclease digest patterns have demonstrated four genetic MCV subtypes designated as MCVI, II, III, and IV with common variability. A high degree of homology between the subtype genomes with highly conserved organization has also been observed. In contrast to the herpes simplex virus (HSV) subtypes, no proliferation association of MCV subtype with site of infection has been noted, despite earlier indication that this might be so.<sup>5</sup>

## Immune Evasion in Molluscum Contagiosum

The immune response to a viral infection is a complex phenomenon that is specific to the organism. Similarly, the MCV also encodes specific molecules to control host defenses and seems to utilize several methods to escape detection by the immune system. Studies have shown that chemokines, like growth-regulated oncogene alpha (GRO) and IL8, are found inside the molluscum lesion as they are released with the clearing of the virus.



Analysis of the MCV genome has revealed more than 70 putative genes that are not seen in other pox viruses, with an additional 100 genes.

The former include a viral homology of cellular chemokines like MCV open reading frame (ORF) with chemokine antagonist activity (mcv148R); others encode A104 amino acid protein with significant homology to a major HLA complex class 1 that binds to beta microglobulin (mc80), subsequently blocking the chemotactic activity of the host chemokines. MCV gene products such as MC53L and MC54L bind IL18 and prevent IFN-gamma production. IL8-binding protein is used as a decoy receptor by the pox virus (MC54 leads to pirating of the receptor).

Other domain proteins that inhibit TNF (MC159, MC160) have been isolated, creating products that inhibit the cellular NF-kappa B protein complex and thus preventing the production of pro-inflammatory molecules and enhancing viral survival. MC66 produces selenocysteine-containing glutathione peroxidase that inhibits peroxidase and UV-mediated apoptosis.<sup>6</sup>

Dermatotropic viruses like HSV produce similar immune evasive proteins thus explaining their persistence.

## Histology

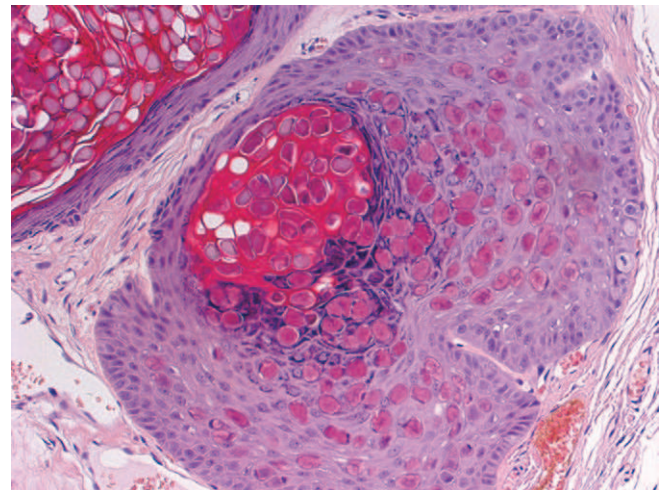
MCV exhibits a lobular proliferation of surface epithelium, showing an aggregation of enlarged keratinocytes that are engorged with viral inclusions (molluscum bodies) usually seen in the centre of the lesion (Fig. 31.1a). The nucleus becomes compressed at the level of the granular cell layer, and the molluscum bodies lose their internal structural markings and develop a homogenous, ground glass, eosinophilic appearance that appears basophilic beyond the granular layer (Fig. 31.1b). Pseudocystic and polypoidal variants of this appearance can be seen in immunocompromised patients. Other histological dermal changes observed are lymphohistiocytic, neutrophilic, or granulomatous infiltrates; the latter mainly seen in solitary MC lesions.

Studies indicate that clinical infection with MCV is not always associated with antibody development though indirect immunofluorescence has demonstrated antibody production in about 70% of patients with visible lesions.<sup>7</sup> Polymerase chain reaction (PCR) can also help detect MCV in skin lesions.<sup>8</sup>

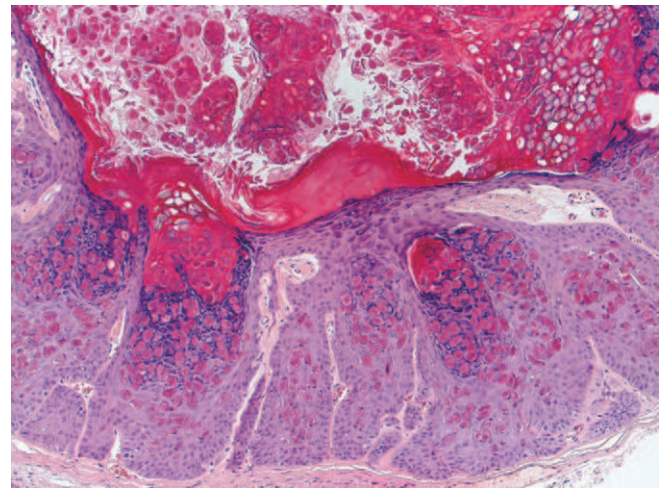
## Epidemiology

This is largely unknown despite the fact that the virus is directly communicable, and large outbreaks have been known to occur. Available studies are few and have focused on rates or risk factors for infection in specific population groups. Others have been defined by geographic locations, age of the subjects, or their immunological status. Providing estimates of population-based incidence rates again is difficult, MC not being a reportable disease. Furthermore, the lack of standardized serological testing, self-limiting nature of clinical infection, and reliance on clinical examination alone for diagnosis limit further detailed study.

As humans are the only reservoir of infection, world-wide distribution is common. A higher incidence of the virus has



\*c+



\*d+

**Fig. 31.1:** (a) Part of an inverted lobule of squamous epithelium showing multiple eosinophilic molluscum inclusion bodies. These extend from above the basal layer to the keratinous debris on the surface (H&E, 10×). (b) At higher magnification (H&E, 20×). Courtesy: Dr. Gerald Saldanha, Leicester Royal Infirmary, UK.

been reported in the tropics, in institutions and crowded areas, and may be related to factors such as warmth, humidity, and poor hygiene.<sup>9</sup>

MC may affect any part of the body. Close sexual contact may be responsible for genital lesions and therefore commonly seen during adolescence and early adulthood. In adults, lower abdominal, thigh, and genital lesions are more frequent than those in extra-genital locations.<sup>1</sup> Studies indicate that for transmission, whether sexual, nonsexual, or via fomites (e.g., sharing bath sponges and towels with MC-infected individuals), close contact is important.<sup>10</sup>

MC is also an important cause of infection affecting the eyelids. Historically, this has been seen exclusively in young children; however, in the recent past this presentation has been increasingly recognized in adults with AIDS. A few isolated

case reports of congenital/vertical transmission exist, though this mode of transmission is uncommon.<sup>11</sup> Autoinoculation, as a mode of transmission, is also suspected.<sup>12</sup>

MC infection typically also occurs in 2- to 5-year-olds<sup>13</sup> and is rarely seen in children below 1 year of age, though a bimodal age distribution has also been described. While the prevalence rates are not known, a study from Netherlands reports one of six Dutch children having visited the doctor for this condition.<sup>14</sup> The same study showed a cumulative incidence rate of 17% in those under 15 years of age, while adult sexually related MC was rare.

MC, when nonsexually transmitted, appears to be more prevalent in the tropics than in Europe. A recent study reported 1.2% of 10- to 12-year-olds from Aberdeen to have the infection, while in Fiji it mainly affected 2- to 3-year-olds with 4.5% of the entire village population affected. In addition, a quarter of all household contacts were affected.<sup>15</sup> Hence, in children the presence of isolated MC lesions is not indicative of sexual abuse unless there are other clues.

Recent reports suggest that rates of MC are on the rise. GUMCAD, a dataset that monitors trends in new diagnosis of STIs in the UK, indicates a 50% increase in MC incidence between 1998 and 2008. Similarly, rates of 20% in female sex workers have been reported from India.<sup>16</sup>

MC is also seen in patients with HIV infection.<sup>17</sup> This association was first reported in 1983 and estimated prevalence rate was 5–18% in the adult group.<sup>18</sup> A recent South African study describes similar rates (21%) in the pediatric HIV cohort.<sup>19</sup> At present, there is little evidence to support MC lesions (mollusca) being more common in people with atopic dermatitis.

The incubation period of MC varies between 19 and 51 days with a wide range of 7 days to 6 months. The period of communicability, while unknown, probably lasts as long as the lesions persist. It is unknown if previous infection confers any protection against subsequent exposure. However, the greater prevalence of lesions in children than adults may suggest the acquisition of subsequent host resistance.<sup>20</sup>

### Clinical Presentation

Primary lesion of MC presents as a papular eruption of several umbilicated lesions with no systemic manifestations. The single discrete lesions are dome shaped and discrete, fleshy, white, translucent, or yellow in color (Fig. 31.2). They are usually smooth, 2–20 in number, and sometimes mistaken for pustules. At presentation, the size of the papules may vary between 2 and 6 mm, depending on the stage of development of the lesion (Fig. 31.3).

### Distribution of Molluscum Contagiosum

Any area may be involved but axillae, ante cubital, popliteal fossa, and crural folds are the favored sites. Mucous membrane involvement is uncommon, though cases with involvement of the conjunctiva and mouth have been described.<sup>21</sup> An eczematous



**Fig. 31.2:** Disseminated and multiple MC lesions seen in HIV infection. *Courtesy: Dr. K. Horn, Bath, UK.*



**Fig. 31.3:** Close view of lesions showing the characteristic umbilication.



reaction may encircle lesions in approximately 10% of patients. Facial lesions as previously described have been reported with HIV infection.<sup>22</sup>

In immunocompromised states, MC may have an atypical presentation in number (>100), in size (>1 cm), in color, and with generalized dissemination.<sup>23</sup> Large sized giant mollusca (>15 cm) and penile horns have been reported.<sup>24</sup> Extensive facial involvement with enlarging lesions is commonly seen; spontaneous resolution being rare in these cases. Lesions also tend to be prolonged, resistant to treatment, and may take 4 years or more to disappear.

In patients known to have HIV infection, the presence of MC may herald advancing immunosuppression or the development of immune reconstitution inflammatory syndrome (IRIS).<sup>25</sup>

It is recommended that the appearance of MC lesions in an adult should raise suspicion and require further evaluation for an immunosuppressed state.<sup>26</sup>

### IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

This is a paradoxical clinical deterioration that is observed in HIV-positive individuals after the introduction of HAART.<sup>27</sup> It represents a diverse range of immunopathological reactions manifesting as improvement of the individual's HIV surrogate markers<sup>28</sup> and immune restoration. Approximately half of these events are dermatologic, the commonest clinical signs reported are herpes simplex infection, herpes zoster, and MC.<sup>29</sup>

### Complications

These are uncommon, though irritation and secondary infection with abscess development have been reported.<sup>30</sup> Disseminated eruptions may also be seen in patients with atopic dermatitis (steroid use, skin trauma, and immunological mechanisms are cited as contributory factors).<sup>31</sup> Occasionally, involvement of the eyelid or conjunctiva may lead to abscess formation.

### Diagnosis

Diagnosis is made on clinical examination, based on the appearance of the characteristic, umbilicated skin lesions (using a magnification lens maybe helpful in some cases).

Histological examination of a curetted or biopsied lesion can help in the diagnosis of difficult cases that are not clinically obvious.

For cytological preparations, the thick white central core can be expressed and smeared on a slide or smears can be made from scrapings of lesions. Smears left unstained or stained with Geimsa, Gram, Wright, or Papanicolaou stains will demonstrate the large brick-shaped inclusion bodies (Fig. 31.1).

Electron microscopy of fixed material from a papule has been used to demonstrate the poxvirus structures of the dumbbell-shaped viral particles.

Immunohistochemical methods using a polyclonal antibody allow recognition of MC in fixed tissue.<sup>32</sup> *In situ* hybridization for MCV DNA has also been utilized.

Laboratory tests for complement fixation, tissue culture, neutralization, and fluorescent antibody are not standardized and not routinely used for diagnosis.

If sexually acquired, MC in adults should raise the possibility of other infections and screening tests for other sexually transmitted infections should be offered.

### Differential Diagnosis

Skin conditions that need to be considered in the differential diagnosis and may coexist with MC are genital warts. Other conditions that simulate the skin lesions are keratoacanthoma, basal cell carcinoma, syringoma, lichen planus, sebaceous adenoma, naevi, histoid leprosy, and varicella zoster virus. Cutaneous cryptococcal infection needs to be excluded in patients with AIDS as an MC-like eruption has been described in several such cases.<sup>33</sup>

### Treatment

Treatment of MC is not needed as spontaneous resolution is the norm in most cases. Patients need to be reassured that the lesions may take a few months to resolve and can be left to heal naturally.

Circumstances where treatment may have to be considered are mainly cosmetic in nature and are cases with underlying atopy.

The goal of treatment is the destruction of the lesion to prevent further transmission and auto inoculation.<sup>34</sup> Most of the available treatments employed traumatize the lesions and speed up the healing process. Antiviral and immune-modulating treatments have recently been added to these options.

Currently, there is no evidence to suggest a superiority of one treatment over another in MC. A recent Cochrane review of treatment interventions (495 patients) highlights that many of the current treatment modalities practiced, including physical destruction, have not been adequately evaluated. Several of the treatments reviewed are not routinely practiced. None of the treatment options had any serious adverse effects. The authors also acknowledge the limitations of the studies as being small numbers of patients, investigators not blinded, and patients not completing the study (were numerous in some studies) excluded in the total analysis.<sup>35</sup>

The choice of treatment is mainly dependent on physicians' experience, patient preference, and the availability of therapy. In view of lack of objective evidence, many of the treatments detailed below are not routinely used in the UK.

*Topical treatments* that have been shown to be effective are discussed below in no particular order of efficacy:

- (a) *Home-based topical treatments* that are currently available include
  - (i) *Podophyllotoxin cream (0.5%)*: Podofilox is an alternative to podophyllin and can be safely self-applied by the patient at home. The treatment consists of the application of 0.05 ml of 5% podofilox in lactate-buffered ethanol twice a day for 3 days.<sup>36</sup> It is important

to ensure that when prescribing for women, adequate contraception is recommended as the use of this agent is contraindicated in pregnancy. Occasionally some irritation may be noted.

(ii) *Imiquimod cream (5%)*: This immunomodulator cream acts by inducing high levels of IFN and cytokines locally and has recently been added as a topical home treatment option to treat MCV. It is self-applied to the affected area nightly for 4 weeks, and patients need to be informed that clearing can take up to 3 months. Though well-tolerated, application site irritation is a common side effect and, like podofilox, its use in pregnancy is not advocated.<sup>37</sup> No toxic effects have so far been reported following its use in children.

(b) *Podophyllin*: This is available as a 25% suspension in a tincture of benzoin or alcohol and contains mutagens such as quercetin and kaempferol. It is applied topically and used once weekly. Its use is advisable under medical supervision as some of the side effects include severe erosive damage in the adjacent normal skin causing scarring. Systemic effects such as peripheral neuropathy, renal damage, adynamic ileus, leukopenia, and thrombocytopenia have been reported with its use, especially on large mucosal surfaces.

(c) *Cantharidin*: This comprises a 0.9% solution of cantharidin and acetone. It is a blister-inducing agent that needs to be applied sparingly to the dome of the lesion with or without occlusion and left in place for at least 4 hours before being washed off. It should be applied only after a test dose on a few individual lesions before treating several lesions, especially those on the face, as treatment has been known to cause severe blistering. If tolerated, treatment is repeated every week or repeated once or twice every 3–4 weeks until the lesions clear. Usually one to three treatments are necessary.

(d) *Tretinoin cream*: Tretinoin 0.1% and 0.05% cream has been successfully used when applied daily or twice daily to the lesions. Erythema of previously treated lesions is a noted side effect though less irritation has been associated with the 0.05% cream.

## Evisceration Methods

An easy method to remove the lesions is eviscerating the core with an instrument such as a scalpel, sharp tooth pick, edge of a glass slide, or any other similar instrument capable of removing the umbilicated core.

- Expression of the pearly core, either manually or using forceps and piercing with an orange stick, with or without the application of tincture of iodine or phenol can also be considered.
- *Iodine solution*: The following technique has been recommended when an iodine solution and salicylic acid is available. 10% Iodine solution is placed on the molluscum papules and allowed to dry, and the site is covered with 50% salicylic

acid plaster. This process is repeated daily until the papules become erythematous, usually in 3–7 days. After this, only the iodine solution is applied. Resolution of lesions has been reported within a 26-day period.

- Similarly, aqueous potassium hydroxide 10% solution can be applied topically to a lesion. Resolution has been seen to occur within a month.
- Tape stripping has been successfully used in treatment and involves the use of an adhesive tape that is repeatedly applied to and removed from the lesion for 10–20 cycles. This removes the superficial epidermis from the lesion but can lead to secondary skin infection.

Because of the simplicity of the above-mentioned techniques, patients, parents, and caregivers may be taught these. These methods, though simple, may not be tolerated by children.

## Cryotherapy with Liquid Nitrogen

Cryotherapy can also be utilized and requires a halo of ice to surround the lesion for maximal effectiveness but can be painful. Repeat applications may be necessary and are carried on a weekly basis. It can be, however, safely used in pregnancy and may need local anesthesia.

## Curettage or Diathermy of the Lesions

Curettage, with and without light electrodesiccation, can be used to treat MC. This method is painful, requiring topical anesthetic cream prior to the procedure. In cases where the diagnosis is uncertain, this may be the preferred treatment method, having the advantage of providing a reliable tissue sample.

## Pulsed Dye Laser

The use of pulsed dye laser has demonstrated some excellent results with reports of 96–99% of lesions responding after just one treatment. It is well-tolerated with no adverse side effects including scarring noted. Majority of the lesions resolve within 2 weeks. However, its prohibitive expense makes it less cost-effective than other options.

## Systemic Drug Treatment

### Cimetidine

This oral histamine<sub>2</sub>-receptor antagonist acts by stimulating the delayed-type hypersensitivity. A single small uncontrolled study has shown resolution in nine out of 13 patients with cimetidine 40 mg/kg/day in two divided doses for 2 months. The use of systemic treatment in treating MC is currently not indicated as the efficacy of cimetidine is still to be determined.

In patients with HIV infection and MC, several studies have shown the introduction of HAART and the subsequent immune restoration leading to the resolution of MC lesions.<sup>38–40</sup>



## Prevention and Control Measures

Patients must be advised to avoid scratching and sharing of grooming implements and personal items. Measures to control the activity of infected cases are not required as the risk of transmission is very low. It may, however, be reasonable to advise/consider suspending an infected individual's sporting activities only in an outbreak situation.

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# Hepatitis Viruses

Gary Brook • Yogesh Chawla

## Hepatitis B Virus

Hepatitis B infection is a global health problem with more than 350 million hepatitis B virus (HBV) carriers worldwide. It is a DNA virus that infects the liver causing hepatocellular necrosis and inflammation. HBV infection can either be acute or chronic, ranging in severity from being asymptomatic to symptomatic and completely resolving to severe, progressive, and even fatal illness.

### MOLECULAR BIOLOGY

HBV is the prototype of hepatotropic DNA viruses (hepadnaviruses). The replication strategy and life cycle of HBV has been studied in animal models, such as woodchuck, duck, and ground squirrel.

### Physical Characteristics

HBV is a hardy virus. Its infectivity persists for many years after plasma storage at  $-20^{\circ}\text{C}$ . It resists heating to  $60^{\circ}\text{C}$  for up to 4 hours, but if heated for 10 hours it would lead to inactivation of a small amount of HBV. Autoclaving and thorough cleansing of equipments, followed by submerging in hypochlorite or glutaraldehyde solution, are good and acceptable methods to inactivate the virus. Three types of viral particles are visualized in infectious sera under electron microscopy.

1. The infectious virion is a 42 nm spherical, double-shelled structure called the Dane particle. The outer shell is the HBsAg (surface antigen), which surrounds the inner core protein (HBcAg, core antigen) containing nucleocapsid.
2. Two other non-infectious particles, which outnumber the Dane particles, are seen as spherical structures of 20 nm diameter and filaments of variable length with a width of 20 nm. These filaments and spheres are composed of HBsAg and host-derived lipids only.

### Genomic Organization

The HBV genome is a partially double-stranded DNA with cohesive 5' ends that maintain a relaxed circular structure.

The viral genome (Fig. 32.1) has a compact organization of four overlapping open reading frames (ORFs) which function as follows:

1. Surface: encodes envelope surface proteins, HBsAg (S-ORF)
2. Core:
  - Precore—encodes HBeAg (C-ORF)
  - Core—encodes HBcAg
3. Polymerase: encodes HBV-DNA polymerase (P-ORF)
4. HBx: a transcriptional activator that probably takes part in oncogenesis (X-ORF).

After an exposure, the virus gains access to the liver *via* the blood. The virus attaches itself to the hepatocyte through

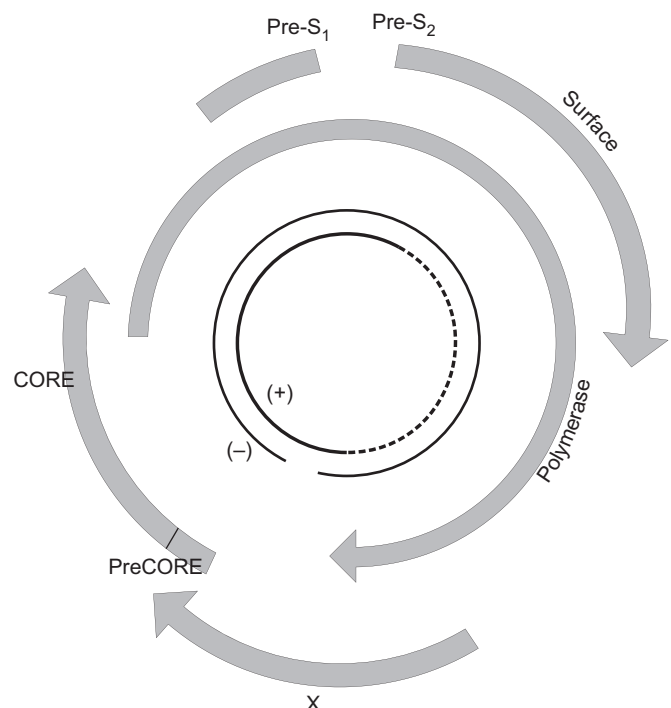


Fig. 32.1: HBV-genome.

the elements of pre-S1 and pre-S2 genes. Sialoglycoprotein receptors on the hepatocyte mediate the uptake of HBV possibly by endocytosis. On entering the hepatocyte, the nucleocapsid is delivered to the nucleus and the viral genome is repaired to form a covalently closed circular DNA (cccDNA). These are transcribed to pregenomic RNA and translated to HBc and *pol* proteins. Viral transcripts are translated in the cytoplasm and the core and polymerase proteins interact with the genomic RNA to form new capsids. Reverse transcription occurs and the mature virions are assembled in the endoplasmic reticulum, where they acquire the surface proteins and are released from the hepatocytes into the circulation by exocytosis.<sup>1</sup> During viral replication, some of the double-stranded HBV-DNA may become integrated into the host chromosomal DNA. This integrated HBV-DNA is possibly responsible for the development of hepatocellular carcinoma (HCC) many years later. The supercoiled cccDNA is not reduced by treatment with reverse transcriptase inhibitors, like lamivudine, which is active only in suppressing viral DNA synthesis and thus HBV replication, but not in eliminating the virion. Thus, these drugs may be suppressive rather than curative. However, cure can occur in patients with suppressed virus through immune clearance. HBV also replicates within the mononuclear cells of the bone marrow or blood, but liver is the primary site of HBV replication.<sup>2</sup>

### HBV Genotypes and HBsAg Subtypes

The genome of HBV is relatively stable. There are seven genotypes A to G based on an intergroup divergence of 8% or more in the complete nucleotide sequence. These genotypes have a geographic distribution as given below:

- A:** Northwest Europe, North America, Central Africa, India;
- B:** China, Japan, Indonesia;
- C:** China, Japan, Korea;
- D:** Mediterranean Basin, Middle East, India;
- E:** Africa;
- F:** American natives;
- G:** United States, France.

Response to antiviral treatment and pathogenesis may vary between different genotypes.

All HBsAg subtype determinants share one common antigenic determinant 'a'. In addition, two pairs of mutually exclusive subtypic determinants 'd' or 'y', and 'w' or 'r' also correspond to typical alleles within the S domain, but they do not clearly correlate with the genotypes. Thus, of the four possible major subtype combinations only three, *ayw*, *adw*, *adr*, have been found with any degree of frequency and these occur in distinct but possibly changing geographic and demographic distribution.

### EPIDEMIOLOGY

The carrier rate of the HBV ranges from 0.1% to 20% in different parts of the world. The HBsAg carrier rate has been found to

be between 1.1% and 12.2% in the general population of India. In high prevalence areas (>8%), i.e., Southeast Asia, South America, and sub-Saharan Africa, perinatal transmission is common, whereas in intermediate prevalence areas (2–7%), like the Mediterranean region, Japan and India, percutaneous and sexual modes of transmission are common. Low prevalence areas (<2%) include northern Europe, US, Canada, Australia, and New Zealand. The mode of transmission in these areas is by the parenteral or sexual route. Several epidemiological studies have reported a decline in the HBsAg carrier rate in western and northern Europe and the United States. This may be due to safer sexual practices, behavioral changes, safe needle practices, vaccination, blood screening refinements, and the use of virally inactivated components.<sup>3</sup> Universal vaccination in some countries has also significantly decreased the HBsAg carrier rate.<sup>4</sup>

### ROUTES OF TRANSMISSION

Transmission of HBV is largely through three routes: vertical (mother to child), sexual, and parenteral.<sup>5–9</sup> In a significant proportion of infected people, the exact route of acquisition is unknown. For transmission to occur, there must be a source, an effective mode of spread and a susceptible host.

### Parenteral Transmission

The source of HBV infection is mostly blood from chronic carriers of HBV. HBV is present in large amounts in the blood, and even a single and minute exposure can transmit the infection. Infectivity correlates with the Hepatitis B viral load in the blood. Patients with HBeAg in addition to HBsAg generally have a higher viral load ( $>2 \times 10^4$  IU/ml), which explains why transmission occurs even with a minor needle stick exposure from an HBeAg-positive individual. Patients who are anti-HBe positive usually have HBV in low titers and thus require a large amount of blood for transmission to occur, except for those with the precore/core-promoter mutant (see below) which can be highly infectious.

HBV has rarely been transmitted from HBsAg negative but anti-HBc positive blood, which represents low levels of infection, such that the virus is present but the HBsAg is in too small amounts to be detected by the routine ELISA kits. Transmission may also occur from HBsAg-negative blood transfusion if the source is in the "window period" of HBV infection.

HBsAg can occasionally be found in very low concentrations in the urine, breast milk, vaginal secretions, cerebrospinal fluid, sweat, tears, bile, and feces, however these secretions have not been proven to be infectious. Semen has been reported to transmit HBV infection (see below), but the amount of virus is 100–1000 folds less than in blood.

Parenteral transmission, thus, can occur after blood transfusions, exposure to untreated plasma products (e.g., factor VIII, factor IX concentrates, and cryoprecipitates), sharps, incidents such as needle-stick injury accidents and exposure to contaminated unsterilized instruments, such as those used in tattooing, acupuncture, ear piercing, or dentistry. Outbreaks of

HBV infection have been ascribed to gynecological surgery or dentistry, when the surgeon is HBsAg- and HBeAg-positive. Transmission has also been reported from HBeAg-negative but HBV-DNA-positive surgeons.<sup>8</sup> Men with hemophilia, who frequently require factor VIII concentrates, had a high incidence of HBV infection in the past before the introduction of treated products and factors created through recombinant technology. Injecting drug abuse is also a recognized source of HBV infection due to the sharing of drug paraphernalia.

## Sexual Transmission

Sexual activity is the most important mode of HBV transmission in areas of low to intermediate prevalence of infection. The manner by which HBV spreads by sexual activity is unclear. HBV is detectable in semen, but spread is higher if there is a break in the skin or mucous membrane of the susceptible host. Thus, the sexual activity most frequently incriminated in HBV transmission has been anal intercourse, especially for the receptive partners.

With heterosexual activity, the spread occurs when HBV in semen or vaginal secretions is probably associated with minute penile or vaginal lacerations. Factors associated with a high risk of viral acquisition in the homosexual population include multiple sexual partners, anal receptive intercourse, and the duration of sexual activity. In the last two decades, as a result of changes in the sexual behavior in response to the AIDS epidemic, viral transmission through this route has decreased considerably in many countries. Presently, heterosexual exposure accounts for the majority of sexually acquired cases in the developed nations. In heterosexuals, factors associated with an increased risk of HBV infection include the duration of sexual activity, the number of sexual partners, a history of other sexually transmitted diseases (STDs), and a positive serology for syphilis.

Sexual partners of injection drug users, commercial sex workers and their clients are particularly at a high risk for infection. Studies of household and sexual contacts of HBsAg carriers have shown that 0–3% of the spouses or sexual partners and 4–9% of the children are HBsAg-positive. More significant is the fact that there is a very high prevalence of markers of prior HBV infection (anti-HBc) in these two groups (30–60% in spouses or sexual contacts and 10–15% in children). These people who are unaware of their infection with HBV form an important source of HBV transmission worldwide. As with perinatal transmission, sexual transmission is also facilitated by active viral replication (high HBV-DNA/HBeAg positivity) in the infected individual.

The use of condoms appears to reduce the risk of sexual transmission. By cloning and sequencing the polymerase chain reaction (PCR)-amplified HBV-DNA, 100% sequence homology of HBV-DNA has been found in both HBV-infected index patients and their spouses. This provides direct evidence of sexual transmission of HBV. HBV appears to be more readily spread by sexual contact than does human immunodeficiency virus (HIV) or HCV as shown by the higher rates of antibodies to hepatitis B than against HIV or HCV among sexual contacts of men with hemophilia and drug addicts.

## Inapparent Transmission

Inapparent spread may occur in the family or in other settings although the route is unclear. This inapparent spread is more likely to occur in children. The role of bed bugs as a source of transmission cannot be dismissed in some countries, although is not proven. In less developed countries, poor hygiene, shared utensils, frequent skin diseases, shared razors, scarification by tribal and traditional healers, tattooing, and acupuncture may spread hepatitis B. The feces of chronic HBsAg carriers is not the source of infection. Infection also does not spread through casual contact, such as touching, hugging, kissing, sharing towels, or food.

## Perinatal (Vertical) Transmission

This is a very important mode of transmission, especially in areas where the HBV prevalence is high. Infection correlates with HBV viral load and is especially high if the plasma HBV-DNA is  $>2 \times 10^4$  IU/ml. The HBsAg positive mother is likely to transmit the infection to the neonate in 90% of cases, if she has a replicative HBV, as detected by HBeAg positivity or a high viral load. The transmission to the neonate is less likely if the mother is HBeAg-negative and has a low viral load. Infected babies are typically asymptomatic and have a 90% chance of developing chronic infection, in contrast to adults who have only 5–10% chance of developing chronicity. The infection is mostly acquired by the infant by inoculation of the infected maternal blood and liquor during passage through the vagina, rather than intrauterine transmission.

## DIAGNOSTIC SIGNIFICANCE OF HBV SEROLOGICAL MARKERS

### HBsAg

If HBsAg is positive for the first time, a second serum sample should be requested to exclude errors. This should be accompanied by IgM anti-HBc, which, if also positive, indicates acute viral hepatitis due to HBV (Fig. 32.2). HBsAg positivity without IgM anti-HBc indicates that the patient is an HBsAg carrier. With current diagnostic assay systems such as enzyme immunoassay (EIA), as little as 1 ng/ml of HBsAg can be detected.

### HBV-DNA

This is the most sensitive test for diagnosing HBV infection, which can be used to clarify issues if the antibody and antigen tests are not completely helpful. The presence of HBV-DNA indicates HBV infectivity. Current assays can detect HBV-DNA to a sensitivity of 50 copies/ml (10 IU/ml). PCR is of use in diagnosing HBV mutants and in determining response to antivirals. It is expensive, which limits its use only to the technologically more sophisticated laboratories.<sup>9</sup>

### HBeAg

HBeAg positivity also indicates infectivity. It is very rare for HBeAg to be positive in the absence of HBsAg (Figs. 32.2 and



32.3). Hence, it should be tested only in patients who are HBsAg positive. However, there are HBV mutations (precore or core-promoter mutants) where the patient can be HBeAg-negative but still infectious with high-titer HBV-DNA.

### Anti-HBe

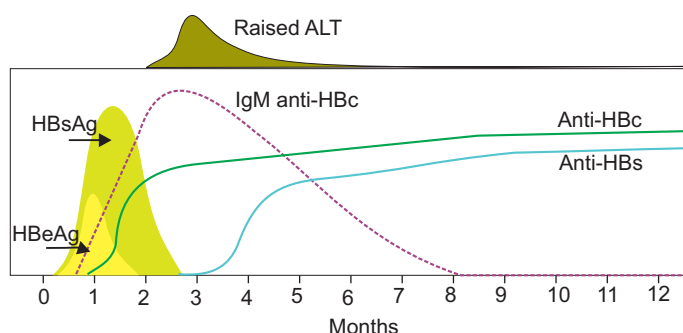
Anti-HBe, in acute hepatitis, generally indicates resolution of the disease and a good prognosis. It may be positive in patients with the precore/core-promoter mutants and HBeAg-negative chronic hepatitis patients. Such patients usually have raised aminotransferases and raised HBV-DNA.

### IgG Anti-HBc

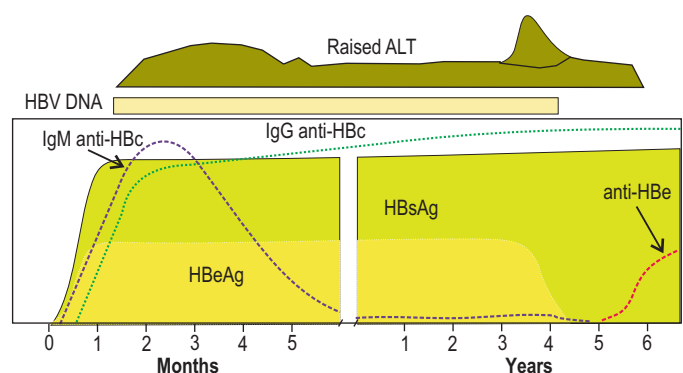
It is found in both active and resolved HBV infections. Testing for anti-HBc is indicated if the prevalence of HBV infection is to be assessed in a community and can also be used as the screening test when testing for HBV infection.

### IgM-Anti-HBc

It is found in acute viral hepatitis B (Fig. 32.2) and its presence is a prerequisite to its diagnosis. It may also be positive in relapsing chronic hepatitis B.



**Fig. 32.2:** Schematic presentation of typical serologic course of acute self-limiting viral hepatitis B.



**Fig. 32.3:** Schematic presentation of typical serologic course of chronic viral hepatitis B.

### Anti-HBs

This is recommended to monitor the success of the hepatitis B vaccination but is also found in people who have recovered from HBV infection.

### PATHOGENESIS

Immunological factors play an important role in causing liver disease due to HBV. Peak HBV replication occurs well before peak cellular injury in acute hepatitis, suggesting that the disease represents immune lysis of infected hepatocytes. The mildest form of liver disease is often seen with the highest concentrations of the virus in the liver and serum, where the liver biopsy may have minimal or even no evidence of cellular necrosis, which suggests that HBV is not a cytopathic virus. The appearance of antibodies to HBsAg, with the disappearance of markers of HBV replication, also demonstrates a role for immunological clearance. A decrease in serum C3 and C4 reflects the formation of antigen-antibody complexes which may be constituted of HBsAg or other antigens of the HBV. Moreover, a strong, multispecific HLA1 and HLA2 restricted T cell response to several viral proteins accounts for cellular injury and viral clearance in acute hepatitis B.

In chronic hepatitis, the HLA class 2 restricted response in peripheral blood is relatively weak and is insufficient to clear replicating virus. In neonates, the suppression of cell-mediated immune response may favor infection, because the exposure to HBeAg induces tolerance to epitopes that are usually the target of cytotoxic T cell response at a time when the immune response is immature.<sup>10</sup> There is also some evidence of a failure of interferon production, which allows the synthesis of viral protein to occur unhindered with a poor display of HLA on the hepatocytes. Chronic infection is more common in immunosuppressed patients, patients on hemodialysis, post-renal transplant recipients, patients with leprosy or leukemia, and those with HIV infection.

### CLINICAL MANIFESTATIONS

The clinical manifestations and outcome of HBV infection depend on the age at infection, the immune status of the host, and the level of HBV replication. The spectrum of HBV infection during the acute phase varies from subclinical hepatitis, anicteric hepatitis, and icteric hepatitis to fulminant hepatic failure. During the chronic phase, it ranges from an asymptomatic carrier state to chronic hepatitis, cirrhosis, and ultimately HCC. The chances of developing chronicity decrease as the age at which HBV infection is acquired increases.

### COMPLICATED CLINICAL COURSE

- **Fulminant hepatitis:** It occurs in <1% and is associated with a high mortality.
- **Post-hepatitis syndrome:** Patients continue to have fatigue, anorexia, but their Liver Function Tests (LFTs) are normal.
- **Relapses:** They can occur in 1–3% of patients who return to full activity rather early or consume alcohol.
- **Chronic hepatitis:** Persistent detection of HBsAg for more than 6 months

## EXTRAHEPATIC MANIFESTATIONS OF HBV INFECTION

Ten to 20% of patients with HBV infection develop extrahepatic manifestations that are believed to be mediated by the immune complexes in circulation.

### Serum Sickness

It is seen in acute hepatitis B as fever, skin rash, arthralgia, and arthritis. This occurs in 5–15% of patients. The rash is urticarial, and arthralgias typically affect the wrist, elbows, knees, and ankles. Morning stiffness is common. Muscle pains and myositis may occur. The arthritis of acute hepatitis begins to improve with the onset of jaundice and resolves completely with no permanent deformity.

### Polyarteritis Nodosa (PAN)

It is rarely a complication of acute HBV infection. Vasculitis affects large- to medium-sized vessels of the cardiovascular system, kidney, gastrointestinal tract, central nervous system (CNS), and skin. Patients present with fever, polyarthralgia, rash, peripheral neuropathy, hypertension, and azotemia. HBsAg can be demonstrated in the vessels.

### Membranous Glomerulonephritis (MGN)

It is found especially in children. Approximately 30% of these children progress to renal failure, whereas 30–60% of children achieve spontaneous remission.

### Papular Acrodermatitis (Gianotti-Crosti Disease)

It usually occurs in young children below 4 years of age. It manifests as a symmetrical, erythematous, maculopapular, non-itchy eruption on the face, limbs, and occasionally the trunk. It lasts for 15–20 days along with axillary and inguinal lymphadenopathy.<sup>13</sup>

### Aplastic Anemia, Red Cell Aplasia, Thrombocytopenia and Agranulocytosis

They have been reported in patients affected with acute viral hepatitis. Pancytopenia usually occurs 2–12 weeks after the onset of jaundice.

### Neuromuscular Complications

They manifest as apathy, irritability, photophobia, and neck rigidity in acute hepatitis. Peripheral neuropathy, cranial nerve involvement, and Guillain-Barré syndrome have also been observed.

### Myocarditis and Pericarditis

Rarely, these have been described as also arrhythmias like atrial fibrillation and ventricular ectopics.

## Pleural Effusion

It can occur rarely that disappears after acute hepatitis has resolved. Acute pancreatitis may occur as a complication of fulminant hepatitis and HBsAg has been detected in the pancreatobiliary secretions.

## ACUTE HEPATITIS B

Only 30–50% of patients have icteric hepatitis, while 50–70% have anicteric or subclinical hepatitis. The course is divided into four phases.

1. **Incubation period:** It ranges from 40 to 140 days, but may be shortened by a large inoculum or prolonged with low-dose percutaneous exposure.
2. **Preicteric/prodromal phase:** This consists of constitutional symptoms, such as malaise, anorexia, nausea, vomiting, low-grade fever, myalgias, fatigue, and altered taste sensations. Some patients have a serum sickness like syndrome with fever, arthralgias (or frank arthritis), and a generalized erythematous maculopapular rash or urticaria. This prodromal period lasts for 3–7 days and is followed by the icteric phase.
3. **Icteric phase:** The constitutional symptoms start decreasing with the onset of jaundice. This period usually lasts for 2–3 weeks, but can be as long as 12 weeks, including a period of itching and clay colored stools.
4. **Convalescent phase:** This begins with the resolution of jaundice. The appetite increases and other symptoms disappear. Fatigue is the last symptom to disappear.

Physical examination in acute viral hepatitis reveals low-grade fever, icterus, and soft tender hepatomegaly. Sometimes, there may be mild lymph node enlargement. Patients with fulminant hepatitis may have features of hepatic encephalopathy and a decreased liver span. In patients with acute viral hepatitis, there is a 10–50-fold elevation in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (ALT > AST). The prothrombin time is a good marker of prognosis. Serum bilirubin level rises to a peak and is also related to prognosis. Rarely, mild leukopenia with relative lymphocytopenia may occur and very rarely findings suggestive of hemolytic anemia may be present. The persistent elevation of ALT for more than 6 months suggests chronic liver injury.

Liver histology reveals lobular disarray, acidophilic degeneration of hepatocytes, focal lobular necrosis, portal and parenchymal infiltration by inflammatory cells (predominantly lymphocytes and macrophages), hypertrophy and hyperplasia of Kupffer cells, disruption of bile ductules, and cholestasis.

## Serological Diagnosis (Table 32.1, Fig. 32.2)

The first serological markers to be detectable in the serum is HBsAg, which appears during the incubation period,<sup>11</sup> HBsAg may last up to 5 months or even longer (Fig. 32.2). Concurrent

**Table 32.1:** Meaning of Serological Marker Results

Stage of infection	Surface antigen (HBsAg)	'e' antigen (HBeAg)	IgM anti-core antibody	Total anti-core antibody	Hepatitis B virus DNA	Anti-HBe	Anti-HBs	ALT
Acute (early)	+	+	+	+	+/++	–	–	
Acute (resolving)	+	–	+	+	+/-	+/-	–	
Chronic (immune tolerant)	+	+	–	+	++	–	–	N**
Chronic (immune active)	+	+	–	+	+	–	–	
Chronic (eAg negative)	+	–	–	+	+	+/-	–	
Chronic (inactive carrier)	+	–	–	+	-/+	+	–	N
Resolved	–	–	–	+	–	+/-	+/-	N
Successful vaccination	–	–	–	–	–	–	+	N

\*In very early infection the IgM anti-core can be negative.

\*\* N=normal.

with, or shortly after the appearance of HBsAg in serum, HBeAg and HBV-DNA become detectable. HBeAg is not found in the serum but is detectable in the liver in some patients with acute hepatitis B. The first antibody to appear during acute HBV infection is IgM anti-HBc that develops shortly after the appearance of HBsAg and persists for 6–12 months. IgG anti-core antibody (IgG anti-HBc) also appears early and often persists for life. Antibody to HBsAg (anti-HBs), which is protective against future infection, usually appears during convalescence after the clearance of HBsAg. The antibody to HBeAg commonly appears with the clearance of HBeAg and HBV-DNA from the serum.<sup>12</sup>

## CHRONIC HEPATITIS B

Five to 10% of adults exposed to HBV and 90% of neonates infected perinatally develop chronic infection. It is more common in men. Only a small percentage of patients with chronic hepatitis give a history of jaundice in the past, because in the majority the onset of infection is asymptomatic or mild. Patients with chronic hepatitis are asymptomatic or may have non-specific symptoms like fatigue that is intermittent, worsens with exertion, but is rarely disabling. They may have other symptoms such as nausea, anorexia, weight loss, jaundice, and low-grade fever. Many patients may be picked up after an executive health check up. With the development of cirrhosis,<sup>14</sup> there is weight loss, weakness, wasting, abdominal swelling, edema, jaundice, encephalopathy, and variceal bleeding. Occasionally, patients may present with HCC. Some patients may present with extrahepatic manifestations of hepatitis B.

There may be no physical signs but hepatosplenomegaly may eventually ensue. With more severe disease/cirrhosis, there may be spider angiomas, edema, abdominal swelling, and signs of portal hypertension, namely splenomegaly, distended veins over the abdomen, and ascites. Endoscopy may show esophageal varices.

Laboratory investigations reveal raised aminotransferases, which may be 5–8 times above the normal, with the alanine

aminotransferase higher than AST and an AST:ALT ratio of <1. Serum bilirubin and albumin are normal, but with increasing severity of liver disease both may become abnormal. With mild disease, the prothrombin time is usually normal, but would become abnormal as the liver disease worsens. If cirrhosis develops, the laboratory results become increasingly abnormal. The AST:ALT ratio becomes >1. Prothrombin time increases and serum albumin decreases with increasing liver dysfunction indicating a poor prognosis. Serological markers in chronic hepatitis B are helpful in defining the stage of infection and predicting the outcome.

Chronic hepatitis B is divided into four types<sup>15–17</sup> (Table 32.2 and Fig. 32.3), namely Type 1 (HBeAg-positive replicative/immune tolerant), Type 2 (HBeAg-positive immune active), Type 3 (low-replicative/inactive), and Type 4 (HBeAg-negative chronic active).

- **Type 1 (immune tolerant):** This phase is characterized by high levels of HBV replication but little or no evidence of active liver disease.

**Table 32.2:** Classification of Chronic Hepatitis B

Patient populations in chronic hepatitis B				
Marker	Immune tolerant (type 1)	Immune active (type 2)	Inactive HBsAg carrier (type 3)	HBeAg-negative CHB (precore/core-promoter mutant) (type 4)
HBsAg	+	+	+	+
HBeAg	+	+	–	–
Anti-HBe	–	–	+	+
ALT	Normal		Normal	
HBV DNA (IU/mL)	$>2 \times 10^4$	$>2 \times 10^4$	$<2 \times 10^2$	$>2 \times 10^3$
Inflammation on histology	Normal/Mild	Active	Normal	Active

- **Type 2 (immune active):** The ALT is high and liver biopsy shows evidence of inflammation and fibrosis. During this phase, spontaneous HBeAg clearance may occur accompanied by biochemical exacerbation (increase in ALT levels).
- **Type 3 (low replicating/inactive):** The virus replication greatly reduces in this phase. HBsAg remains positive. The ALT levels are normal, HBV-DNA levels are low, and the resolution of necroinflammation, as seen on liver biopsy, occurs. The annual rate of clearance of HBsAg is between 0.5% and 2% per year.<sup>16</sup>
- **Type 4 (HBeAg-negative chronic active):** Some patients may lose HBeAg and still have raised aminotransferases and HBV-DNA. These patients have precore/core-promoter mutant HBV and is common in Italy and Greece, but rare in the US and UK.<sup>17</sup> This is not as benign as was previously thought and 15–20% of patients ultimately develop cirrhosis in 5–20 years.

## Development of Hepatocellular Carcinoma

HCC is common in countries where chronic HBV infection is common. It occurs decades after the development of chronic hepatitis B. It is more common in men and in patients who acquire HBV infection in childhood. These patients present with a mass in the abdomen, decompensated liver disease, bleeding, or constitutional symptoms characteristically seen with any malignancy. About 80% have pre-existing cirrhosis but in 20% HCC arises in non-cirrhotic liver due to direct carcinogenic effects of HBV.

Abdominal imaging, such as ultrasound, is the most sensitive screening test. HCC can also be diagnosed by serum alpha-fetoprotein (AFP) although it is less sensitive than liver imaging. A progressive increase in AFP should raise suspicion of HCC in a chronic hepatitis B positive patient.

## TREATMENT

### Acute Hepatitis B

Patients with acute viral hepatitis are managed with supportive treatment. Most cases of acute viral hepatitis eventually resolve with the clearance of the virus and complete healing of the hepatic injury. However, in very severe cases with impending acute liver failure (ALF) antivirals, such as telbivudine, lamivudine, or entecavir, are indicated.

### Chronic Hepatitis B

The aim of treatment is to achieve sustained suppression of HBV replication and remission of liver disease. There are seven therapeutic agents approved for treatment of chronic hepatitis B with more under trial.<sup>18–23</sup>

#### Pegylated Interferon Alpha

The interferons have antiviral, antiproliferative, and immunomodulatory effects. Therapy with pegylated interferon

is indicated in patients who are (i) HBeAg positive with raised enzymes and (ii) HBeAg negative, HBV-DNA positive with raised enzymes (HBV precore/core-promoter mutants).

A response (virological) is achieved in 33–37% of patients, after pegylated interferon alpha therapy weekly for 48 weeks. HBsAg loss in these responders occurs in 7.8% of cases.<sup>18,19</sup> Nevertheless, a sustained response as demonstrated by normalization of transaminases and HBV-DNA clearance can be achieved in 15–25% of patients with mutant HBV (HBeAg-negative chronic hepatitis B), but long-term follow-up has shown a clearance of HBsAg in 15–30% of these sustained responders.<sup>20</sup> Interferons are expensive, which limits their use in resource poor areas. The response to interferon is likely to be poor in HBeAg-positive patients with normal enzymes and immunosuppressed individuals.

Interferons have complications like reversible bone marrow suppression. Flu-like symptoms are common, appear 4–6 hours after injection and diminish or disappear over 2–3 weeks of therapy, are dose dependent, and can be easily controlled with paracetamol. Psychiatric symptoms, such as irritability, anxiety, depression, psychosis, and suicidal attempts, that may be potentially dangerous, occur in 3–5% of patients. Rarely, acute renal failure, acute myocarditis, and bacterial infection may occur. Interferons are contraindicated in patients with concomitant severe extrahepatic illness, myelosuppression, thyroid dysfunction, psychiatric disorders, and autoimmune diseases.

HIV co-infection with HBV worsens the prognosis of liver disease and reduces the response rate to interferons.

#### Nucleoside Analogues

These drugs interfere with HBV replication by inhibiting the reverse transcriptase.

**Lamivudine (3TC)** It is effective although when used as monotherapy, resistance occurs at a high rate. It incorporates active triphosphate into the growing DNA chains, resulting in premature chain termination, thereby inhibiting HBV-DNA synthesis. It is of use in patients who are (i) HBeAg positive with raised aminotransferases, (ii) HBeAg negative, HBV-DNA positive with raised transaminases (mutant HBV), (iii) non-responders to interferon treatment, and with (iv) HBeAg-positive cirrhosis.

HBeAg to anti-HBe seroconversion and a marked reduction in HBV-DNA occurs in 17–32% of patients with an HBsAg loss of <1%, ALT normalization is seen in 41–72% of patients and histological improvement in 49–56% of patients. It is given in a dose of 100 mg orally, daily and should be administered for at least 1 year as a shorter duration of therapy is associated with lower rates of HBeAg seroconversion. A problem with lamivudine is the development of resistance that occurs in 14–32% of patients and manifests as a breakthrough infection defined as the reappearance of HBV-DNA in serum after its initial disappearance. It has a limited role in treating HBV infection due to its resistance profile.



**Adefovir** Given at a dose of 10 mg daily leads to HBeAg seroconversion to anti-HBe in about 15% after 48 weeks but will suppress HBV-DNA in 25–50% with 50% histological improvement and ALT normalization on long-term treatment. Resistance is much less common than with lamivudine, making it suitable for long-term suppressive treatment.

**Entecavir** It is very effective at a dose of 0.5 mg daily for treatment naïve patients and 1.0 mg daily for those with lamivudine-resistant HBV. 60–90% will show HBV-DNA suppression, 21% HBeAg to anti-HBe seroconversion, and 70% shows daily histological and ALT improvement after 48 weeks therapy. Acquired resistance is uncommon making this drug suitable for long-term suppressive therapy.

**Telbivudine** Although this drug, given at a dose of 600 mg daily, is very effective in the short-term, with a therapeutic response of about 70%, it is more prone to inducing resistant mutations than most of the other drugs and at a rate (28% at 2 years) which is only modestly less than lamivudine. It is therefore not suitable as long-term suppressive mono therapy.

**Tenofovir** This agent is more widely known and used for the treatment of HIV. At a dose of 300 mg daily it has an efficacy and barrier to resistance profile similar to entecavir. It is especially suitable, when given as part of triple anti-retroviral therapy, for the treatment of HIV/HBV co-infection.

**Emtricitabine (FTC)** Like tenofovir, this is an anti-HIV drug which is effective against HBV and is widely used in combination with tenofovir for the treatment of HIV/HBV co-infection as part of triple anti-HIV therapy. Its efficacy and resistance profile is similar to lamivudine. It is being considered as a treatment for HBV monotherapy.

**Combination Therapies** There is some evidence that combinations, such as adefovir plus lamivudine, may be more efficacious and lead to less resistance. However, the outcomes of clinical trials are awaited to clarify their status.

**HIV Co-infection** Most of these drugs have anti-HIV activity. Tenofovir, 3TC, FTC, and entecavir are all known to cause drug-resistant HIV if used as monotherapy. Telbivudine may also cause HIV treatment resistance although this is less clear. The only drugs that can be given alone in patients with HIV/HBV co-infection are adefovir and pegylated interferons. It is therefore crucial that all patients with HBV infection should receive an HIV test prior to starting therapy to prevent inadvertent induction of HIV drug resistance.

## PREVENTION

Hepatitis B vaccines are highly effective and provide protection against hepatitis B by stimulating the production of neutralizing antibodies against HBV.<sup>24</sup> Immunization reduces the incidence of hepatitis B by 90–95%.<sup>25</sup> Protection occurs with a rise in anti-HBs titers within weeks of the first 1–2 doses of vaccine. Protection titers for anti-HBs are >10 mIU/ml.<sup>26</sup> The vaccination can be

used for preventing perinatal transmission, where the vaccine should be administered within 12 hours of birth. In mothers who are HBeAg positive, hepatitis B immune globulin should also be given to the baby soon after birth.<sup>27</sup> The vaccine gives protection against HBV infection to an immunized individual for at least 5–10 years. Symptomatic hepatitis B is not observed in these immune individuals even if the anti-HBs levels fall to undetectable levels. This indicates that the vaccine establishes a good immunological memory and therefore some authorities suggest that the vaccine confers lifelong immunity after successful immunological response.

Subunit vaccines containing recombinant HBsAg produced in yeast have replaced the chemically inactivated HBsAg particle vaccines that were produced from chronic HBsAg carriers (plasma-derived vaccines). These recombinant vaccines are comparable in terms of safety and efficacy and adverse effects are fewer. Anaphylaxis is a rare complication. An immunization course includes three doses of the vaccine given at 0, 1, and 6 months or 0, 1, 2, and 12 months. Immune response may be reduced in persons over 40 years of age or those who are otherwise immunocompromised. These patients may benefit from a second course of vaccine or double doses of vaccine. Anti-HBs titer estimation is not routinely recommended following immunization except in high-risk individuals. The most effective strategy for controlling HBV infection is universal vaccination. In Taiwan, after universal vaccination, there has been an 80% fall in chronic HBV carriage in children, with similar decrease in childhood liver cancer.

## Hepatitis C Virus

Hepatitis C virus (HCV) was identified and characterized in 1989 by molecular techniques from chimpanzees infected with sera from humans with chronic non-A, non-B hepatitis. The virus is notorious for causing persistent infection in almost 85% of the patients leading to chronic hepatitis. These patients are likely to develop cirrhosis and HCC.<sup>28,29</sup> It is an enveloped virus belonging to the Flaviviridae family with a single-stranded RNA genome.

## GENOMIC ORGANIZATION

The HCV genome is a positive sense, single-stranded RNA of approximately 9.4 kb in length, with a single large ORF and highly conserved untranslated regions (UTRs) at the 5' and 3' ends (Fig. 32.4). There is little available detail on the replication cycle of HCV, as the virus undergoes a low-level replication in any cell culture system studied. B and T cell-derived lymphoid cell lines may permit HCV replication to a limited extent.<sup>30</sup> Significant heterogeneity has been observed among different HCV isolates leading to at least 6 genotypes identified as HCV 1 to HCV 6 and subtypes identified by lower case letters a, b, etc., based on the extent of nucleotide sequence divergence.<sup>31</sup> The genetic heterogeneity of HCV occurs because the HCV replication *via* the viral RNA polymerase is error prone, as the replicase lacks a proof reading exonuclease.

C	E1	E2	NS2	NS3	NS4A	NS4B	NS5A	NS5B
Core (C)	–	Nucleocapsid						
E1 and E2	–	Envelope proteins						
NS2A	–	Membrane-associated protein						
NS2B	–	Metalloproteinase activity						
NS3	–	Serine proteinase, nucleotide triphosphatase and RNA helicase						
NS4A	–	Cofactor for NS3 proteinase						
NS4B	–	Function not known						
NS5A	–	Interferon sensitivity sequence						
NS5B	–	RNA-dependent RNA polymerase						

**Fig. 32.4:** Hepatitis C virus genome showing encoding regions and functions.

### EPIDEMIOLOGY<sup>31–35</sup>

The worldwide prevalence of chronic hepatitis C is 0.5–2.0% accounting for 150 million carriers in the world. All the genotypes are distributed in different geographic areas throughout the world. HCV 1 and HCV 2 are common in West Africa, Western Europe, North America, Australia, and Japan, HCV 3 in India, HCV 4 in Central Africa and Egypt, HCV 5 in South Africa, and HCV 6 in South East Asia. The infection is more prevalent in men, and there is evidence of age-related distribution of infection with minimal prevalence in childhood and progressively rising figures with increasing age.

The prevalence of anti-HCV is higher in high-risk groups (transfusion dependent) such as thalassemics (42–83%), men with hemophilia (50–95%), hemodialysis recipients (10–45%), injecting drug users (48–90%), tattooed persons (11%), prisoners (15–46%), and alcoholics (15–25%).<sup>32</sup> The prevalence of chronic HCV infection in patients with chronic hepatitis, cirrhosis, and HCC is very high in Europe and Japan (60–90%), intermediate in United States, Australia, and Africa (30–60%), and lower in China and other countries of the Far East (10–30%).

### ROUTES OF TRANSMISSION

HCV is efficiently transmitted by blood and blood products.

### Transfusion-Associated Transmission

In the past, HCV accounted for 85% of post-transfusion hepatitis, but this has now declined to 4%.<sup>36</sup> This is due to the exclusion of paid donors and the HCV screening of blood. It is still possible to miss some HCV-positive blood, if the donor is in the incubation period, for which screening with HCV-RNA would be needed. The risk is higher in transfusion-dependent hematologic disorders, such as thalassemia or hemophilia, but this has now been taken care of with the use of mandatory blood testing for HCV.

### Non-transfusion-Associated Percutaneous Transmission

#### Injecting Drug Use

Injecting drug use with the sharing of needles, syringes, and other paraphernalia is the most commonly identified risk factor

for HCV infection. Fifty to 80% of injecting drug users become anti-HCV positive within 12 months of initiating drug use and almost all are anti-HCV positive by 8 years.<sup>37</sup>

#### Healthcare Workers

Seroprevalence in healthcare workers ranges from 0.6% to 4.5% in some countries,<sup>38</sup> with dental surgeons having the greatest risk. Healthcare workers exposed to HCV positive blood after accidental needle sticks have an average seroconversion rate of 1.8% (range 0–6.6%).<sup>38,39</sup>

#### Hemodialysis

In the past, sharing of hemodialysis machines led to an increase in HCV infection among patients with renal failure. Nowadays, patients are routinely tested and if positive, for HCV, use machines designated for infected patient to prevent infection of those who are uninfected.<sup>40</sup>

#### Transplantation

Chronic HCV complicates hemodialysis patients at the time of renal transplantation.<sup>41</sup> The risk of acquiring new HCV has been reported to be up to 10% in the uninfected patients following transplantation, especially those receiving more than 5 units of blood or more than one kidney. About 50% of the organ recipients from donors positive for antibody to HCV develop hepatitis after transplantation, and therefore this is an exclusion criterion for donation.<sup>42</sup>

### Non-percutaneous Transmission

#### Sexual

The non-percutaneous modes of transmission include transmission between sexual partners and transmission from a mother to her offspring. The available evidence indicates that for HCV, as against HBV, transmission by non-percutaneous routes is inefficient and rare. This holds true for sexual transmission also.

Overall, the risk of HCV transmission with sexual activity is not clearly defined. Most sero-epidemiological studies have demonstrated anti-HCV in only a small number of sexual contacts of those who are HCV positive. In prospective studies of the sexual partners of HCV-positive people, the rate of transmission has been seen to be less than 1% per year, whereas HIV and HBV are transmitted much more readily. It is evident that sexual transmission is an important route of acquisition of HBV and HIV, but not of HCV.

Using PCR genomic amplification, the presence of HCV-RNA has been reported in saliva, vaginal secretions, and seminal fluid of infected subjects.<sup>43</sup> The results of these studies have been variable, because of the presence of possible inhibitors in the biological fluids, the levels of viremia and the number of HCV infected mononuclear cells in the studied samples. The risk of infection in the spouse of an HCV-infected person in a long-term monogamous relationship is about 4% (range, 0–27%).<sup>44</sup> Even in female sexual partners of men with hemophilia who

are infected with HCV, anti-HCV is detected in no more than 3–6%. In a Japanese study of spouses of 154 index patients with chronic hepatitis C, 27 (18%) were found to have HCV-RNA in the serum. Genotypic analysis was identical in 24 of the 27 pairs, suggesting transmission from the index patient to the partner. Another factor that has been found to determine the sexual transmission of hepatitis C is the pattern of sexual relationship. Sexual partners of index subjects without high-risk behavior (injection drug use or promiscuity) have anti-HCV prevalence ranging from 1 to 10%. In contrast, sexual partners of subjects with high-risk behavior have anti-HCV prevalence between 11 and 27%. Data also suggest that the sexual transmission of HCV, from male to female, may be more efficient than *vice versa*, which is similar to other blood borne viruses.<sup>45</sup>

Thomas et al.,<sup>46</sup> in a study of 309 non-injection drug using STD patients, found that 7% of the men and 4% of the women had anti-HCV. In logistic regression analyses, factors associated with anti-HCV positivity included age, greater numbers of lifetime sex partners, and HIV infection. Women, whose sex partners were anti-HCV positive, were 3.7 times more likely to have anti-HCV than those having anti-HCV negative partners. The proportion of RNA homology between anti-HCV positive females and their male partners was higher (94%) than among randomly selected patients (82%). The presence of genital ulcerations seems to increase the risk of sexual transmission of the HCV. Weinstock et al. have found that having sex with an injecting drug user having a history of gonorrhea and syphilis was associated with anti-HCV positivity on univariate analysis, but after controlling for confounding variables no such associations remained.<sup>47</sup>

Homosexual men have a higher rate of anti-HCV positivity as compared to monogamous heterosexual contacts. However, in this group, unidentified injecting drug use and multiple sexual exposures cannot be excluded. In a study of homosexual men, it was found that sexual risk factors for anti-HCV positivity included anal receptive intercourse, having an injecting drug using sexual partner, history of genital herpes, and HIV seropositivity. Sexual transmission of HCV in homosexual men is significantly increased as compared to the population controls, if the number of partners is more than 50. In the last decade, there has been a steady rise in many parts of the world of acute HCV infection in HIV-positive homosexual men and this is linked to traumatic anal sex, co-infection with ulcerative STDs [syphilis, herpes, lymphogranuloma venereum (LGV)], and recreational drug use.<sup>48,49</sup>

Sexual partners of injecting drug users (6%),<sup>50</sup> prostitutes and their clients (3.5–9% and 16%, respectively)<sup>51</sup> and heterosexuals with multiple sexual partners<sup>52</sup> have all been reported to be at an increased risk. The presence of HIV as co-infection enhances the sexual transmission of HCV.<sup>52,53</sup> The prevalence of anti-HCV and anti-HIV antibodies among female sexual partners of multi-transfused hemophiliac men was 2.6 and 12.8%, respectively. The risk of transmission of HCV was seen exclusively in those couples in whom the men were positive for both HCV and HIV antibodies. Thus, all women who were anti-HCV positive also had co-infection with HIV. The transmission of HIV alone was

not affected by the presence of co-infection with HCV in the male spouse. The authors concluded that the higher prevalence of HCV occurs in female sexual partners of men with hemophilia who have the co-infection of HCV with HIV.<sup>53</sup> The frequency of HCV transmission to sexual partners is 5 times higher when HIV is also transmitted, suggesting that HIV may be a cofactor for the sexual transmission of HCV. Sexual transmission of HCV in this setting is probably more effective because of enhanced viremia as a result of immunosuppression. In HIV positive individuals, the presence of injecting drug use further enhances the risk of acquisition of HCV infection. Overall, the data indicate that the sexual transmission of HCV does seem to occur, though rather inefficiently. The risk of acquiring HCV infection after a single sex act is negligible in most people although it can be high in HIV-positive homosexual men with high-risk sexual practices. Transmission of the HCV probably depends mainly on the viral load and that the level of viremia in most patients infected by HCV is probably insufficient for an effective sexual transmission.

### Perinatal Transmission of HCV<sup>54–57</sup>

In contrast to the high efficiency of perinatal transmission of hepatitis B from mother to infant, the rate of perinatal transmission of HCV infection is only 2–8%. High titers of circulating HCV in the mother may place the infant at a greater risk of acquiring HCV infection. A higher rate of perinatal transmission (36–44%) has been reported from mothers co-infected with HCV and HIV. Further studies are needed to delineate the time of infection (*in utero* or at the time of birth), the importance of breast feeding in neonatal transmission and the natural history of perinatally acquired HCV infection.

### Sporadic HCV Infection

One of the most vexing epidemiological questions is how HCV is acquired in approximately 40% of the patients, without identifiable risk factors.<sup>57</sup> Despite the screening of voluntary blood donors by questionnaires designed to exclude patients with risk factors for HCV infection, 0.5% are found to be anti-HCV positive. Sporadic HCV infection may result from a prevalent non-percutaneous or percutaneous route yet to be identified.

## NATURAL HISTORY OF HCV INFECTION<sup>58–63</sup>

This is largely based on previous studies of post-transfusion hepatitis, which reveals the silent nature of acute and chronic infections, precluding detection in the early stages of disease.

### Acute HCV Infection

It presents as asymptomatic transaminitis 2–26 weeks after exposure. The enzymes are elevated more than 15 times in 75% of patients. Less than 30% patients are symptomatic with constitutional symptoms such as anorexia, weight loss, abdominal pain, myalgia, and minimal jaundice. The symptoms are often indistinguishable from those due to hepatitis A or B. These symptoms usually resolve



over 1–3 months. Fulminant hepatic failure with HCV is extremely uncommon. HCV-RNA is the first to become detectable by PCR in acute hepatitis C infection, as early as 1 week after exposure. The antibody response to HCV is detected 4–8 weeks after exposure although it may be delayed for 3 or more months. Risk of chronicity has been estimated to be around 60–70%.

## Chronic HCV Infection

Only about one-third of patients have symptomatic liver disease, which is indistinguishable from other chronic liver diseases. Fatigue is the most common symptom followed by right-upper abdominal pain. Physical examination may reveal hepatomegaly in 30–70% of patients and splenomegaly in up to 15%. Jaundice is present in only 1% of cases. Patients in whom cirrhosis have developed may have a palpable liver, spleen, and stigmata of chronic liver disease. Serum ALT levels are normal in up to 30% of the patients, but there is a wide variability in enzyme elevation when patients are followed over time.

The histological features of chronic hepatitis C cover a spectrum of lesions ranging from non-specific and mild changes to chronic lobular, chronic persistent, and chronic active hepatitis with or without superimposed cirrhosis. Chronic hepatitis C usually displays less portal and periportal inflammatory activity and more lobular and degenerative changes. Macrovesicular steatosis, sinusoidal cell activation, eosinophilic granules, and bile duct lesions are the other lesions characteristically seen in patients with chronic hepatitis C.

Chronic hepatitis C exists in two different forms:

### 1. HCV carrier state with normal aminotransferases:

These patients are identified either during blood donation or at screening for HCV. Histologically, two-thirds of the patients show evidence of chronic hepatitis with one-third displaying normal to non-specific changes. These patients more commonly have genotype 2 or 3 and have a lower HCV-RNA load in the serum and liver and on follow-up may show an elevation of liver enzymes.

### 2. HCV carrier state with raised aminotransferases:

These patients have an unpredictable course. They may either have mild histological changes in the liver and are clinically asymptomatic, or may progress to severe liver disease that is symptomatic. The progression from acute hepatitis to cirrhosis or development of fibrosis may take 3 to 30 years. ALT values do not always predict the histological severity of the lesion. The outcome is more severe in patients infected via blood transfusion due to a larger virus inoculum and higher HCV replication as compared to those acquiring HCV through injecting drug use. Histology of the liver is the most adequate way to assess the stage and progress of chronic hepatitis, as most biochemical and virological parameters, like HCV genotypes, have uncertain prognostic values. More recently, transient hepatic elastography, an ultrasound-based technique to assess liver fibrosis, has been shown to correlate well with the results of liver biopsy.

Chronic hepatitis C is a slowly progressive disease with minimal clinical deterioration during the first 1–2 decades after infection.<sup>61</sup> However, survival in patients with decompensated cirrhosis is poor with only about 50% surviving for more than 5 years. HCC is a significant complication of HCV infection with the mean duration of HCV infection being 28–29 years and an annual risk of 1.4% in low-prevalence regions to 6.9% in high-prevalence areas, such as Europe and Italy.<sup>61,62</sup> The cofactors affecting the progression of HCV include alcohol intake that accelerates liver injury and probably also viral replication, male gender, age more than 45 years, ethnicity, host immune status, genotype 1b, and coexisting HIV infection.<sup>63–68</sup>

## EXTRAHEPATIC MANIFESTATIONS OF HCV

Chronic HCV has been associated with a number of extrahepatic disorders:

- **Autoantibodies:** Overall, 40–65% of patients with chronic hepatitis C are positive for antinuclear antibody, smooth muscle antibody, and anti-thyroid antibodies in low titers that represent an epiphenomena.<sup>69</sup>
- **Essential mixed cryoglobulinemia (EMC):** *Anti-HCV* is found in 42–54% and HCV-RNA in up to 84% of patients with essential mixed type II cryoglobulinemia. HCV-RNA has been demonstrated in the cryoglobulins of these patients. It is more frequent in patients with long-standing disease and suggests the chronic stimulation of B cells for the production of immune complexes. Clinically, EMC presents in 10–25% of patients as a triad of palpable purpura, arthralgias, and weakness with involvement of lungs and CNS. Interferon therapy results in decreased levels of cryoglobulins and an improvement in skin lesions.<sup>70</sup>
- **Cutaneous leukocytoclastic vasculitis (CLV):** It is probably the most common mixed cryoglobulinemia (MC)-related extrahepatic manifestation of chronic hepatitis C. It occurs in the presence of MC in 40–95% of such patients. The vasculitis appears as palpable purpura mostly on the lower extremities and can result in frank ulceration. It occurs as a result of the plugging of dermal capillaries with precipitated cryoglobulins.<sup>71</sup> HCV virus has been found in the IgG and IgM complexes and the severity of CLV correlates with the level of viraemia.<sup>72</sup> Such patients should be treated with interferon, which may eradicate the detectable virus.
- **Cryoglobulinemic renal disease:** Membranoproliferative glomerulonephritis has been reported in chronic HCV infection, both with and without MC, whereas MGN has been described only in patients without MC. Twenty percent of patients with chronic hepatitis C infection and MC have renal involvement, which is associated with a worse prognosis.<sup>73</sup> Interferon therapy is helpful.
- **Arthralgias:** Almost 50% of patients with chronic hepatitis C infection and mixed cryoglobulins complain of arthralgias, polymyositis, dermatomyositis, Behçet's syndrome, anti-phospholipid syndrome, and fibromyalgias. In a series from Israel, 31% of the 90 HCV patients had musculoskeletal symptoms.<sup>74</sup> Occasionally, patients with chronic hepatitis C and MC pres-



ent with arthralgias and high serum titers of rheumatoid factor and a mistaken diagnosis of rheumatoid arthritis is made. Joint involvement is usually non-migratory and symmetric. Ankles, wrists, elbows, hands, and toes are most commonly involved. These patients respond to antiviral therapy.

- **Neuropathies:** MC, in association with chronic hepatitis C infection, causes peripheral neuropathy in 10–20% of cases<sup>75</sup> manifesting as paraesthesias. The underlying vasculitis has been held responsible for cerebral infarction, stupor, mononeuritis multiplex, and cranial nerve palsies.
- **Pulmonary vasculitis:** These patients are extremely ill with multi-organ damage and develop respiratory failure that is progressive and refractory to treatment.
- **Sjögren syndrome:** Fourteen percent of patients with Sjögren syndrome have evidence of HCV infection.<sup>74</sup>
- **Porphyria cutanea tarda PCT:** This is the most common form of porphyria, which is characterized by the over production of porphyrins and their precursors. In France, Italy, and Spain, 70–90% of patients with PCT have been found to have chronic hepatitis C.<sup>69,76,77</sup> The prevalence is, however, less in Australia and New Zealand, where only 0–20% of patients with PCT have chronic hepatitis C infection. Possibly, HCV precipitates PCT by the production of antibodies against hepatic uro-D, an enzyme necessary in porphyrin metabolism. It is also due to virally induced oxidative stress and reduction in the redox potential of the hepatocytes.<sup>78,79</sup>
- **Lichen planus:** A 29% incidence of anti-HCV in patients with lichen planus was found from Italy compared to 3% in controls and 12% for hepatitis B.<sup>80</sup> Studies from UK have failed to reveal any association. The prevalence of HCV infection in patients with lichen planus thus varies from one geographic area to another.<sup>81</sup>
- **PAN:** It is rarely found in patients with chronic hepatitis C. In these patients anti-HCV positivity should be confirmed by HCV-RNA, because of likely false positivity for antibody testing. The prevalence of anti-HCV antibodies of 5–20% has been reported in patients with PAN.<sup>82</sup>
- **Prurigo:** This association has been known with chronic hepatitis C infection, as 11 out of 28 patients with prurigo (39%) had HCV infection as compared to only 5% of the controls.<sup>83</sup>
- **Other manifestations:** Urticaria, prurigo, erythema nodosum, and erythema multiforme have been occasionally reported in association with chronic hepatitis C.<sup>83</sup> An increased association of HCV and non-Hodgkins B cell lymphoma,<sup>79</sup> autoimmune thyroiditis,<sup>79</sup> lymphocytic sialadenitis with xerostomia,<sup>84</sup> and autoimmune thrombocytopenic purpura<sup>85</sup> have also been described.

## DIAGNOSIS<sup>85</sup>

HCV infection can be diagnosed by tests for antiviral antibodies (anti-HCV) and the direct detection of the virus genome in the serum, infected tissues and cells, and characterization of the genomic sequences of the virus to define the genotype and subtype.

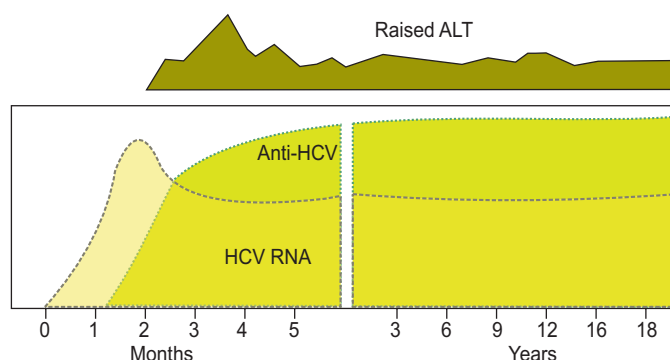
- **Anti-HCV:** Serum antibodies are formed against a variety of non-structural and structural HCV antigens (Fig. 32.5). It is useful to diagnose past and present infection. Over the years, the sensitivity of ELISA kits to detect antibodies to HCV has improved. The third generation ELISA kits that incorporate antigens from NS3, NS4, and NS5 region have a very high sensitivity, except in patients who are in the early phase of infection before seroconversion or are immunocompromised. In these patients, serum HCV-RNA detection needs to be done for diagnosis. False-positive reactions are seen in patients with hypergammaglobulinemia, systemic lupus erythematosus, alcoholic liver disease, and metabolic disorders, as well as in pregnant women.
- **Serum HCV-RNA:** HCV-RNA is detected by PCR usually with primers derived from the more conserved 5' UTR of the viral genome.<sup>86</sup> HCV-RNA is helpful in diagnosing patients in the early phase of acute hepatitis C before seroconversion (Fig. 32.5), in immunosuppressed individuals, in patients with autoimmune disorders, those with hypergammaglobulinemia, and those on treatment with antivirals.
- **HCV genotyping:** This may help in prognosticating and planning the duration of antiviral therapy. HCV 1b genotype is more commonly seen in patients with severe liver disease including cirrhosis and HCC. These patients respond less well to therapy. Patients with the HCV 2 and 3 genotype are more frequently asymptomatic carriers with normal aminotransferases.

## TREATMENT

The aim of the therapy is to eradicate the HCV virus, thereby reducing liver injury, so that cirrhosis and HCC are delayed or prevented.

## Acute Hepatitis C Infection

More and more evidence is available that such patients should be treated with pegylated interferon alpha. One of the problems, while initiating treatment in acute hepatitis, is picking up such cases, as most of them are asymptomatic. A study, published by Jaeckel et al.<sup>87</sup> showed a 98% HCV-RNA clearance in 44 patients with acute hepatitis.



**Fig. 32.5:** Schematic presentation of typical serologic course of acute viral hepatitis C progressing to chronicity. HCV-RNA appears first in serum, followed by anti-HCV. ALT levels do not correlate with the activity and extent of liver damage.

## Chronic Hepatitis C Infection<sup>88–90</sup>

Treatment is with weekly pegylated interferon alpha plus daily ribavirin. Response rates of about 45% for genotypes 1/4 and 75–80% for genotypes 2/3 can be expected. Firstly, the decision has to be made about who to treat. For genotypes 2/3 all suitable patients should be offered treatment where available as the response rate is so high. Relative contraindications to therapy include psychiatric illness, continuing injecting drug use and severe illness including decompensated cirrhosis. For genotypes 1/4, given that the response rates are lower, therapy can be deferred if the liver disease is mild with little or no fibrosis on liver biopsy or hepatic elastography. Otherwise patients with liver fibrosis of grade 2 (Ishak score) or higher should be treated. The duration of therapy varies according to the viral genotype and virological response. The response is highest in patients with a rapid virological response (RVR) when the HCV-RNA is <50 copies/ml after 4 weeks therapy and with early virological response (EVR) when the HCV-RNA is <50 copies/ml or has fallen by  $>2 \times \log_{10}$  after 12 of weeks therapy. In genotypes 1/4 patients may be treated for 24 weeks if there is an RVR or 48 weeks if there is an EVR. If an EVR is not achieved, therapy can be stopped as it is unlikely to work. In genotypes 2/3, patients may be treated for 16–24 weeks if there is an RVR or 24 weeks if there is an EVR. If an EVR is not achieved, therapy can be also stopped as it is unlikely to work. In general, patients who are also HIV-positive have a lower response rate although this can be improved by ensuring that the CD4 count is as high as possible when treatment is started and by giving longer durations of treatment.

## Hepatitis A Virus

Hepatitis A virus (HAV) is a major public health problem throughout the world causing acute infection in millions of people every year. It is largely spread through the feco-oral route although it can be spread sexually in restricted circumstances. It is a small unenveloped RNA virus which is similar to the picornavirus family but is classified now in the hepatovirus genus.

## GENOMIC ORGANIZATION<sup>91</sup>

The HAV genome is about 7500 nucleotides long of positive sense RNA. It is polyadenylated at the 3' end and there is a VPg polypeptide at the 5' end. It comprises a single ORF which accounts for most of the genome and encodes for a single large polyprotein. This polyprotein is broken down to produce both structural and non-structural polypeptides. Replication takes place in the cytoplasm of the host hepatocyte. There is a single serotype but it can be divided into seven genotypes. However, there is a single dominant conserved epitope that stimulates neutralizing antibodies. HAV is resistant to environmental and acid degradation.

## EPIDEMIOLOGY<sup>92</sup>

HAV is endemic worldwide and the major route of transmission is feco-oral through food, water, and close personal contact.<sup>94–98</sup> Parenteral spread has been reported in injecting drug users, men with

hemophilia using contaminated factor VIII and other recipients of blood products.<sup>94–98</sup> These high-risk groups for parenteral exposure have in common a significant prevalence of chronic HBV and HCV infection. In patients with chronic hepatitis B or C or any other chronic liver disease, acute HAV infection can cause severe hepatitis leading to fulminant hepatic failure.

The disease severity and likelihood of symptoms is very much age-related.<sup>92</sup> For instance, only 5–20% of children under 5 years old will develop jaundice during acute infection and HAV-related mortality is rarely seen in this age group. In highly endemic countries, infection typically occurs at a young age and therefore is usually without symptoms. Conversely, adult-acquired infection is much more frequently associated with symptoms including jaundice (possibly 75–90% of cases), though mortality remains generally very low at around 0.3%. Thus, HAV infection is associated with significant morbidity and greater risk of mortality when it occurs in older patients and in those with underlying chronic liver disease.

The worldwide prevalence of hepatitis A can be divided into five groups (Table 32.3). The WHO also recognizes three levels of HAV prevalence.<sup>92</sup>

## High Endemicity<sup>93</sup>

Developing countries with poor sanitary/hygienic conditions—parts of Africa, Asia, and Central and South America. Infection is mostly in children and therefore usually mild or asymptomatic. Disease incidence may reach 150/100,000 population per year with approximately 1 million cases per year in these areas.

**Table 32.3:** Patterns of Hepatitis A Endemicity

HAV endemicity	Epidemiological patterns by region	Average age of patients (years)	Usual routes of transmission
Very high	Africa, parts of South America, the Middle East, and of south-east Asia	Under 5	1. Person to person 2. Contaminated food and water
High	Brazil's Amazon basin, China, and Latin America	5–14	Person to person Contaminated food and water Outbreaks
Intermediate	Southern and Eastern Europe, some regions of the Middle East	5–24	Person to person Contaminated food and water Outbreaks
Low	Australia, USA, and Western Europe	5–40	Common source outbreaks
Very low	Northern Europe and Japan	Over 20	Exposure during travel to high-endemicity areas, uncommon source

## Intermediate Endemicity

Countries where sanitary conditions are variable—South and East Europe, parts of the Middle East. Many children escape infection, therefore clinical disease incidence may be high as infection occurs more frequently in adults.

## Low Endemicity

Countries with good sanitary and hygienic conditions—Northern and Western Europe, Japan, Australia, New Zealand, USA, and Canada. Infection rates are low and disease tends to occur among specific risk groups. Disease incidence of 5–10/100,000/year.

Improving levels of sanitation in many countries in the last decade have led to a fall in childhood HAV infection with a concomitant rise in adults susceptible to symptomatic disease and outbreaks.

## ROUTES OF TRANSMISSION

Feco-oral (via food, water, close personal contact) is the major route of transmission.<sup>94–98</sup> Outbreaks have been reported in men who have sex with men, linked to oro-anal or digital-rectal contact, multiple sexual partners, anonymous partners, sex in public places and group sex.<sup>99–105</sup> However, several seroprevalence studies in the UK, Spain, USA, and Italy show a similar rate of hepatitis A (IgG) antibodies in homosexual and heterosexual men.<sup>103,106,107</sup> HIV-positive patients are not at increased risk but may be more infectious.<sup>108,109</sup> Outbreaks have also been reported among injecting drug users, in institutions for people with learning difficulties, and in contaminated batches of factor VIII.

Patients are infectious for approximately 2 weeks before and 1 week after the jaundice by the non-parenteral routes but virus can be found in the blood and stool until after the serum aminotransferase levels have peaked.<sup>23</sup> In HIV-positive patients, Hepatitis A (HAV) viremia may continue for over 90 days.<sup>18</sup>

## Sexual Transmission

Men who have sex with men (MSM) are the group for whom there is the best evidence of sexual transmission of HAV, with numerous outbreaks reported.<sup>9–15</sup> In MSM, risk factors for HAV infection include visits to saunas and darkrooms, sex with anonymous partners, group sex, oro-anal and digital-rectal intercourse, and number of partners. The actual mechanism of sexual transmission remains uncertain but is presumably feco-oral and related to oral, penile, or digital contamination during sex. Reported outbreaks have been mainly confined to large cities including Melbourne, New York, London, Amsterdam, and Tokyo. However, the majority of MSM do not acquire HAV infection this way and there are several studies showing a prevalence of HAV-IgG (an indicator of past infection with hepatitis A) that is no higher in MSM than in heterosexual men attending STI clinics. For these routes of transmission, condoms are unlikely to prevent infection. There

is no evidence for heterosexual spread of HAV. As HAV is largely a childhood infection in many countries, unsurprisingly there is also no evidence for sexual transmission as a significant route of infection in adults in resource-poor countries.

## NATURAL HISTORY OF HAV INFECTION<sup>110–113</sup>

The incubation period of HAV is 2–6 weeks. Symptoms of acute hepatitis start with a ‘flu-like prodromal illness’ (malaise, myalgia, fatigue), often with right-upper abdominal pain which can last for 3–10 days.<sup>114</sup> This is normally followed by icteric hepatitis (jaundice) for a few weeks which rarely lasts longer than 3 months. The jaundice is a mixed hepatic and cholestatic type and is associated with anorexia, nausea, and fatigue which usually last for 1–3 weeks. It can persist for 12 or more weeks in a minority of patients who have cholestatic symptoms of itching and deep jaundice.<sup>115</sup> Fever is not found in this phase.

Illness is very much age-related in HAV infection with only 5–20% of children under 5 years old showing symptoms. Adults are more likely to develop symptomatic hepatitis (75–90%) although the mortality is generally very low at around 0.3% of cases. HAV infection has a higher mortality when it occurs in patients over 40 years or those with chronic liver disease such as that due to hepatitis B, C, or alcohol. HIV does not influence the course of the illness.

Physical signs are non-specific in the prodromal phase with the patient showing evidence of fever and looking generally unwell. In the icteric phase, jaundice with pale stools and dark urine will be found. Liver enlargement/tenderness and signs of dehydration are also common. The fever will normally have resolved by the 3rd day of jaundice.

Complications of hepatitis A are relatively uncommon. ALF complicates approximately 0.4% of cases. Of those with acute icteric hepatitis, about 15% may require hospital care, of whom a quarter will have severe hepatitis (Prothrombin time [PT] > 3 seconds prolonged or bilirubin >170 mmol/L).<sup>116,117</sup> ALF due to hepatitis A is more common in patients already infected with chronic hepatitis B or C, although studies differ widely in measured rates.<sup>116,118</sup>

Chronic infection (>6 months) has only been reported in a tiny number of case reports.<sup>119</sup> The overall mortality is <0.1% although it rises to 40% on those with ALF unless they receive a liver transplant.<sup>116,117</sup> In pregnancy, the infection does not have any teratogenic effects but there is an increased rate of miscarriage and premature labor, proportional to the severity of the illness.<sup>120,121</sup> There have been case reports of possible vertical transmission.<sup>120,122,123</sup>

## EXTRAHEPATIC MANIFESTATIONS OF HAV

Extra-hepatic manifestations are very rare. There are reports of Henoch–Schönlein purpura and one case of cardiac failure attributed to hepatitis A.<sup>124,125</sup>



**Table 32.4:** Biochemical Features of Acute Viral Hepatitis

Test	Notes
Serum aminotransferases (ALT, AST)	Normally peak at 500–10,000 IU/L within the first 2 weeks. Takes up to 2–12 weeks to become normal
Serum bilirubin	Can be raised to >100 µmol/L. The bilirubin is both conjugated and unconjugated with bilirubinuria detectable. Prolonged jaundice may be seen in patients with the cholestatic variant of hepatitis. Jaundice may persist after aminotransferases settle
Serum alkaline phosphatase	Usually normal or only mildly raised (<300 IU/L) except in the uncommon cholestatic variant of acute viral hepatitis
Prothrombin time	May be slightly prolonged by 1–5 seconds. Prolongation >5 seconds (INR >1.5) reflects more severe liver damage and identifies patients who may be at risk for development of hepatic failure

## Diagnosis

Appropriate biochemical tests for suspected acute viral hepatitis are listed in Table 32.4. There are two serological tests for HAV: HAV-IgM and HAV total antibody.<sup>126–128</sup> (Table 32.5). In acute infection, the serum IgM anti-HAV antibody becomes positive during the prodromal illness and persists for up to 6 months.<sup>125–127</sup> Thus, positivity is indicative of recent infection. The total HAV antibody test becomes positive also within the prodromal illness but persists for many years and therefore a positive test does not distinguish between acute and past infection. Contacts of known cases (sexual, household, or other close contact) should also be tested. A positive total HAV antibody test signifies that the person is immune to hepatitis A.

### Screening of Asymptomatic People

At the STI clinic, the aim of screening is to identify those at risk by their sexual behavior in order that they may be offered vaccination if non-immune. Some clinics may choose to screen all MSM men. Others may choose to screen those MSM men

at highest risk, i.e., those living in areas where HAV in MSM is prevalent and also if they meet one or more of the following criteria: more than two partners within 3 months, anonymous partners, sex in public venues such as saunas or 'dark rooms', group sex, oro-anal, or digito-rectal sex.<sup>99–105</sup>

As injecting drug users are also at risk and may attend STI clinics as their only contact with health services, they also should be screened and vaccinated. The screening test for asymptomatic patients is serum total HAV antibodies and a positive result indicates natural immunity with no need for vaccination. If non-immune patients are vaccinated then there is no need for subsequent screening.<sup>126,128</sup> However, if vaccination is contraindicated or may not have worked (for instance in someone with HIV infection), then those with continuing risk should be asked to return for repeat tests should symptoms suggestive of acute hepatitis ensue in the future.

## TREATMENT

As most cases are mild or asymptomatic, treatment is normally based on rest and hydration. It is important to isolate patients as much as possible from people who are non-immune. There are no specific anti-viral treatments and so for severe cases, it is again a matter of supportive therapy. In the rare cases of ALF, supportive therapy should be offered in a specialized liver treatment unit with access to liver transplantation if available.

In pregnancy, women should be advised of the increased risk of miscarriage/premature labour and the need to seek medical advice if this happens.<sup>120,121</sup> Breast feeding can be continued and most children will have mild or asymptomatic infection.

## PREVENTION

Vaccination should be offered to all at risk.<sup>129–135</sup> If there is exposure to a known case of hepatitis A within the period 2 weeks before to 1 week after the onset of jaundice, post-exposure prophylaxis can be performed for at-risk household contacts or homosexual contacts (oro/anal, digital/rectal, and penetrative anal sex). The Hepatitis A vaccine schedule comprises doses at 0 and 6–12 months achieving 95% protection for at least 10 years (Table 32.6).<sup>129–135</sup> Current advice is to revaccinate after

**Table 32.5:** Confirmatory Serum Tests for Viral Hepatitis (Common Patterns)

Virus type	Acute infection	Chronic infection	Recovered/Immune
Hepatitis A	IgM anti-HAV +ve	Does not occur	IgG anti-HAV +ve. IgM anti-HAV –ve
Hepatitis B	IgM anti-HBc +ve, HBsAg +ve, HBeAg +ve, HBV-DNA +ve	IgM anti-HBc –ve (+ve low titer in flares) HBsAg +ve, HBeAg + or –ve, HBV-DNA+ or –ve	IgG anti-HBc +ve IgG anti-HBs +ve (may become negative) HBsAg –ve
Hepatitis C	IgG anti-HCV +ve by EIA (but may take up to 3 months or more). HCV-RNA +ve by PCR	As for acute infection	Antibody negative or IgG anti-HCV +ve by EIA. HCV-RNA –ve by PCR
Hepatitis D	IgG and IgM anti-HDV +ve HDAg +ve, HDV-RNA +ve With markers of acute/chronic hepatitis B infection	As for acute infection	Antibody, antigen, and RNA tests become negative within months of recovery



**Table 32.6:** Vaccine Schedules

Vaccine	Schedule	Advantages
Hepatitis A+ B	0, 1–6 months	90% or more response
	0, 1, 2, 12 months	May get a response within 3 months
	0, 1, 3 weeks, 12 months	May get a response within 1 month
Hepatitis A	0, 6 months	Fewer doses than the A+B vaccine

10 years<sup>128–135</sup> although there is increasing evidence that vaccine-induced immunity may be >20 years and possibly lifelong, so no further booster doses may be needed after the primary course in immunocompetent patients.<sup>129–135</sup>

The vaccine is formaldehyde-inactivated HAV grown in human diploid cells and is available as a single formulation or combined hepatitis A & B and hepatitis A & typhoid vaccines. All formulations seem to be equally efficacious.<sup>129–135</sup> They are given intramuscularly into the deltoid (not buttock) or subcutaneously if there is a bleeding disorder. In HIV-negative recipients, 95–100% will respond to a course of vaccine in terms of disease prevention. The commercially available test for serum total HAV antibodies is not sensitive enough to detect vaccine-induced immunity so vaccine response cannot be confirmed in clinical practice. Response rates to vaccination in HIV-positive people is reduced and this correlates with the CD4 count, with best response at CD4 counts >500 cells/mm<sup>3</sup>.<sup>136–138</sup> If patients with a low CD4 count (<300 cells/mm<sup>3</sup>) are vaccinated, they should be revaccinated if the CD4 count rises above 500/mm<sup>3</sup> as a result of highly active antiretroviral therapy or if the HAV IgG remains negative on retesting.<sup>136–138</sup> There is a low rate of mild injection-site reaction and rare transient systemic illness following vaccination and those with allergy to the vaccine or its components should not be vaccinated. There is also a combined A plus B vaccine which is given at 0, 1, and 6 months or 0, 1, 3 week and 12 months. Manufacturers recommend booster doses after 5 years although it is now widely held that in immune-competent patients boosters are not required (see above).

Given the unreliable attendance by many people using STI clinics it is best to give the first dose of vaccine at the initial clinic attendance to all those at risk of infection, especially if there is no history of prior vaccination or disease. The serum total HAV antibody test should be measured at the same time and the vaccination schedule can be continued or not, depending on whether this test subsequently shows the recipient to have been previously infected. Many patients at risk for HAV are also at risk for hepatitis B and so the combined A plus B vaccine would be an appropriate choice. However, if it is felt that the patient may not return for further doses then monodose HAV and monodose HBV vaccines should be administered as they contain more antigen and are therefore more likely to be effective after a single dose.

Human normal immunoglobulin (HNIG) 250–500 mg intramuscularly should also be considered for patients at higher risk of complications (concurrent chronic hepatitis B or C,

chronic liver disease or age >50 years), (Ib, A).<sup>129–131,133</sup> HNIG that is effective against HAV is in short supply and may only be available from public health authorities. HNIG works best if given in the first few days after first contact with an efficacy of 90% and is unlikely to give any protection more than two weeks after first exposure, but may reduce disease severity if given up to 28 days after exposure.<sup>129</sup> Patients are most infectious for two weeks before the jaundice (i.e., before the illness is recognized).

There is a combined Hepatitis A+B vaccine given on the same schedule as the hepatitis B vaccine and has similar efficacy to the individual vaccines although early immunity to hepatitis B may be impaired (IIa, B).<sup>139,140</sup> If an outbreak is suspected or if the index case is a food handler, notify the local public health department by telephone.

### Summary

The hepatitis viruses A, B and C are a major public health problem throughout the world causing acute and chronic infection in millions of people every year. All three infections can be spread sexually in specific circumstances. This chapter describes the three individual types of hepatitis in terms of their epidemiology, disease spectrum, and prevention.

Hepatitis A is caused by an RNA virus that is primarily transmitted by the feco-oral route but has also been shown to spread in sexual contact between men who have sex with men causing acute icteric hepatitis. Unlike hepatitis B and C, chronic infection is not a complication of this infection. Prevention is based on vaccination and hygiene.

Hepatitis B is caused by a DNA virus that is most commonly spread on a worldwide basis via the mother-to-child route although the sexual and parenteral routes are also important. It is equally infectious via unprotected penetrative vaginal and anal sex, mostly from chronic carriers. Approximately 5% of adults infected with hepatitis B will become chronic carriers although this rate is considerably higher in younger people and the immunocompromised. A significant minority also progress to liver cancer. This explains why there are approximately 350 million carriers worldwide, a million hepatitis B-related deaths each year and why liver cancer is one of the world's top 10 cancers. A further complication of hepatitis B is hepatitis D co-infection. This is often seen after parenteral transmission but sexually transmitted cases are being increasingly recognized. Hepatitis D leads to a more rapid progression toward cirrhosis and liver cancer. Both hepatitis B and D can be prevented by vaccination. Sexual transmission is additionally prevented through safer sex such as the uniform use of condoms.

Hepatitis C is caused by an RNA virus that is mostly spread via the parenteral route, especially in injecting drug users. Sexual transmission is largely confined to men who have sex with men and linked to frequent partner change, traumatic anal sex, and concurrent ulcerative STIs such as herpes, syphilis, and LGV. Acute infection is most often asymptomatic but about 80% of those infected become chronic carriers. With over 130 million carriers worldwide, this infection is also a leading cause of cirrhosis, liver cancer and death. There isn't an effective vaccine and so prevention is based on advice to those at risk- safer injecting practices for IDUs and safer sex for MSM.

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## Introduction

Human cytomegaloviruses (HCMVs) are ubiquitous herpes viruses producing a variety of human infections in all age groups. The name of the virus is derived from its property of producing large intranuclear inclusions and smaller cytoplasmic inclusions, resulting in massive enlargement of the infected cells. It is a widespread opportunistic pathogen that causes no obvious clinical manifestation in healthy individuals. On the other hand, it poses an important public health problem because of the high frequency of congenital infections resulting in serious birth defects. Infections acquired after birth are generally mild and range from asymptomatic subclinical infection to a mononucleosis like syndrome in normal individuals but may be fatal in immunocompromised patients.

## History

Knowledge regarding this virus (Table 33.1) goes back to 1904 when big inclusion bearing cells were observed in the kidney, lung, and liver of infants who died of some disease, which was mistaken as congenital syphilis.

## Biology

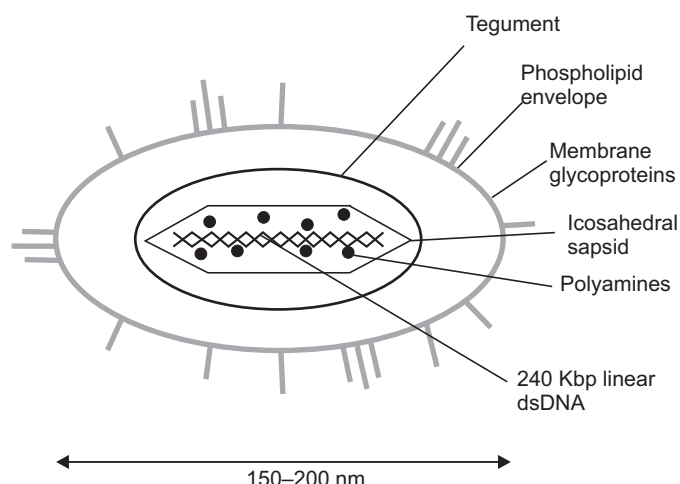
### MORPHOLOGY

HCMV belongs to the family Herpesviridae, which are the largest DNA viruses grouped under  $\beta$  herpes viruses. It has the same

**Table 33.1:** History of Nomenclature of Cytomegalovirus

Year	Nomenclature
1904	<i>Entamoeba mortinatalium</i> (protozoa)
1921	Cytomegalia—large inclusion bearing cells in tissues
1926	Viral etiology—salivary gland virus
1956	Isolation of virus from human tissues
1960	Cytomegalovirus*

\*The term “cytomegalovirus” was proposed by Weller and colleagues to replace the term “salivary gland virus” which was misleading because the virus also involved other organs.



**Fig. 33.1:** Human CMV virion structure.

general structure as those of herpes viruses and demonstrates icosahedral symmetry. The size of the virus is 150–200 nm, significantly larger than that of herpes simplex virus (HSV). It has a 240 kb linear double stranded DNA genome, coding more than 70 viral proteins and has around 200 potential open reading frames.<sup>1,2</sup> The virion has a protein capsid, surrounded by a lipoprotein envelope containing a lipid bilayer and a number of virally encoded proteins (Fig. 33.1).<sup>3</sup> Between the capsid and the envelope is an amorphous layer referred to as the tegument. A cell surface glycoprotein, located within the tegument, acts as an Fc receptor that can nonspecifically bind to the Fc portion of immunoglobulins. This protein helps in immune evasion by the virus.<sup>4</sup> Antigenically related but genetically different strains of HCMV circulate in the human population. However, this may not have many clinical implications. HCMV can be distinguished from other herpes viruses by certain biologic properties such as host range and the type of cytopathology induced.

It has been demonstrated that HCMV contains not only DNA but also four species of mRNA, indicating that this virus is more complex than previously believed.<sup>5</sup> The virally encoded mRNAs are transcribed from one immediate early (IE) gene,

two early genes, and one late gene. Other herpes viruses may also contain similar types of mRNAs within their virions. However, classification of the herpes virus family will be affected by identification of viruses containing both DNA and RNA. It will be of great interest to virologists to discover the function that the virion mRNAs themselves or their protein products play in HCMV pathogenesis and may lead to new targets for treatment of herpes virus infections.<sup>6</sup>

## REPLICATION

HCMV replicates preferentially in human fibroblast cells *in vitro*. In laboratory cultures, it displays slow cellular replication, restricted cell tropism, limited cell to cell infection, and the presence of virulent virus within the cell. These *in vitro* properties of HCMV may reflect its limited pathogenicity in the normal human host. Cultures have to be incubated for a prolonged period, up to 50 days, as the cytopathic effects (CPEs) are slow in appearing. *In vivo*, the virus replicates in epithelial cells, especially in salivary glands, renal, and respiratory epithelium.<sup>7</sup> Replication is seen in the cell nucleus and it can cause either a lytic and productive or a latent infection. Large nuclear and smaller cytoplasmic inclusions are produced during replication.<sup>8</sup>

HCMV attaches to heparan sulfate receptors on the plasma membrane surface. As there are a variety of cell types susceptible to HCMV, it is possible that either there are a number of cellular receptors to which it can attach or they are distributed all over.<sup>9</sup> Penetration into the host cell involves fusion of plasma membrane and viral envelope. After penetration, the nucleocapsid is released into the host cell cytoplasm.<sup>9</sup> In the cytoplasm, the mRNAs are translated into proteins in the absence of gene products encoded by viral DNA. However, the function(s) of the mRNAs or their products is unknown. HCMV virions are then transported to the vicinity of the nucleus, where virus gene expression starts. Like other members of the herpes virus family, HCMV expresses three sets of genes,<sup>3</sup> i.e., immediate early (IE), early, and late genes. IE genes are first to be expressed. Their protein products have regulatory function in determining the expression of the next set of genes.

## Pathogenesis

The pathogenesis of HCMV infection is complex and starts with the penetration of the virus into the cell. Following infection, the virus resides in endothelial cells, macrophages or granulocyte stem cells.<sup>10</sup> Evading host immunity, it replicates to produce viral progeny. This is followed by spread of the virus to new cellular hosts within the body and to most of the organs.<sup>11</sup> Peripheral blood monocytes and circulating endothelial cells have been reported to be responsible for hematogenous spread.<sup>12</sup> Direct cell to cell contact has also been reported as mode of spread.

Like all herpes viruses, HCMV establishes a life long latent infection. Virus can be shed intermittently from the pharynx

and in the urine for months to years after primary infection. Latency is achieved after the acute phase of infection. Latent state in seropositive individuals is presumably maintained by the host immune response. Recently, bone marrow progenitor cells of the granulocyte/monocyte lineage have been shown to be the site of HCMV latency.<sup>13</sup> Besides this, HCMV has been shown to reside in vascular endothelial cells and bone marrow stromal cells.<sup>14</sup> Despite being thought to lie completely latent, the virus can be isolated from 61% of saliva samples,<sup>15</sup> 10% of uterine secretions, and 37% of urine samples<sup>15</sup> and is also found in blood, semen, vaginal secretions, milk, and stool.<sup>16–18</sup> This suggests that like HIV infection, the virus may occasionally cause a smoldering subclinical infection.<sup>19</sup>

The virus interacts with the host in the development of latency and further reactivation and replication. The latter occurs during favorable conditions and results in cellular damage.<sup>3</sup> This is caused either directly by viral lytic action or the host immune response. HCMV chorioretinitis in severely immunocompromised AIDS patients<sup>20</sup> is due to direct CPE of the virus. Immune mediated injury is the primary pathologic mechanism in HCMV pneumonitis.<sup>21</sup> Both direct and indirect mechanisms can combine to develop certain other manifestations.

Reactivation of HCMV is common and the virus is shed in various body secretions such as urine, saliva, semen, breast milk, and cervical fluid. The monocytes carrying HCMV in the latent state adhere to activated vascular endothelial cells. Next, they migrate into tissues where they differentiate into macrophages, thereby reactivating HCMV from the latent state and causing local CPE and intercellular transmission.

Reactivated infections are associated with disease more often in immunocompromised patients than in normal hosts. Depending upon the degree of immunosuppression, severity of reactivated infections varies from mild to severe. HCMV cooperates with other viruses by suppressing cell mediated immunity (CMI) and causing recurrences.<sup>22</sup>

HCMV infection in the fetus or in the newborn can be acquired from the mother with both primary and reactivated maternal infection. Maternal viremia may result in fetal infection in approximately one out of three cases of primary HCMV infection occurring during pregnancy. Although the most common cause of congenital infection is believed to be transmission of reactivated virus *in utero*, it seldom causes fetal damage. Generalized cytomegalic inclusion disease is the result of primary maternal infection. The greater severity of primary neonatal HCMV infection<sup>23</sup> might be explained by the facts that (i) latently-infected mothers give their children both virus and protective maternal IgG, (ii) viral titers are greater during primary infection so that infants receive more virions or perhaps, (iii) as in HIV infection, the virus evolves within the host because virions from primary infection are more virulent. The maternally derived immune response to HCMV determines both the frequency of transmission of the virus to the fetus (25–75%) and the virulence of ensuing infection. The finding that preconceptional serologic immunity can dramatically lower the rate of fetal infection but

not completely prevent intrauterine transmission, is unique to HCMV.<sup>24</sup>

## Host Immune Response

Immune response to HCMV infection is both humoral as well as cell-mediated and these along with natural killer (NK) cells play an important role in the immune control of HCMV disease.

### HUMORAL RESPONSE

Different types of antibodies to a variety of immunogenic HCMV proteins appear in human sera after infection. Most human sera have antibodies to envelope glycoproteins *gB* and *gH* and also to phosphoproteins.<sup>25,26</sup> Neutralizing antibody is mainly directed against the above glycoproteins and is associated with protection from infection and disease.<sup>27–29</sup> In organ transplant patients, HCMV infection is more frequent and severe when the donor is seropositive and recipient seronegative. Pretransplant immunization with live HCMV vaccine<sup>30</sup> and passive immunization with high-titer HCMV immunoglobulin<sup>31</sup> may prevent infection or reduce the severity of the disease in renal transplant patients. Maternal antibodies do not confer any protection against viral transmission as transplacental infection is probably carried by infected cells and is associated with high viremic load. However, development of serious disease can be prevented by maternal antibodies. Presence of antibodies in the breast milk does not prevent transmission to the neonate. Polyclonal activation of B cells by the virus contributes to the development of rheumatoid factors and other auto-antibodies during HCMV mononucleosis.<sup>8</sup>

### CMI

Both CD4+ and CD8+ T cell responses are found in seropositive patients. However, the CD8+ cytotoxic T lymphocyte (CTL) response is prominent and pivotal in the host defence against HCMV.<sup>32</sup> CD4+ T cells are necessary for the generation of this response.<sup>33</sup> Primary infection in late childhood or adulthood is often associated with a strong CTL response, resulting in the development of mononucleosis like syndrome. These CTL responses may contribute to immunopathology by reacting with the human leukocyte antigen molecules induced by HCMV. Progression of disease is associated with HCMV specific CTL responses.

There is some degree of immunosuppression associated with acute infection. During immunosuppression, the likelihood of reactivation from latency causing a variety of disease conditions is dependent on the viral load.<sup>34</sup> Antithymocyte globulin, a potent suppressor of CMI, may cause clinical HCMV syndromes.<sup>8</sup> Prevention of infection was achieved by successful transfer of CD8+ HCMV specific CTLs to immunocompromised bone marrow transplant recipients.<sup>35</sup> CTL immunotherapy has been found to decrease the viral DNA load in the organs and also

reduce the recurrence rate. However, complete DNA clearance could not be achieved.<sup>36</sup> HCMV may function as a cofactor to activate latent HIV infection.

### TARGET PROTEINS

Of all HCMV specific CTL responses, 70–90% recognizes the tegument protein pp65, which constitutes 95% of the tegument.<sup>37,38</sup> In addition, glycoprotein B (*gB*), the major envelope glycoprotein and pp150-tegument protein are also identified as targets.

### NK CELLS

The role of these cells in HCMV immunity was suggested by a case report of a NK cell deficient patient with severe HCMV and other herpes virus infections.<sup>39</sup>

### IMMUNE EVASION

HCMV may evade host's immune response resulting in the persistence of productive infection, viremia, and virus excretion for months or years.<sup>40</sup> This may be due to HCMV gene products that are responsible for this interference through several immunological mechanisms at different stages of the viral replication cycle.<sup>41,42</sup> Immune evasion strategies can be evasion of antigen presentation via interaction with cytokines or evasion of complement and humoral immunity.

## Epidemiology

The disease is endemic in all parts of the world, although it is never seen in epidemic form. Human beings are the only known host for HCMV. The prevalence of infection varies with socioeconomic status, living conditions, and hygienic practices. In developed countries, antibody prevalence varies from 40% to 80% in adults in high socioeconomic groups. In contrast, a prevalence rate of 90–100% in children and adults in developing nations and also in low socioeconomic groups in developed countries have been reported.<sup>3</sup> Overcrowding, poor personal hygiene, probable contact with infected urine and frequent breast feeding of infants may contribute to the high seroconversion rate.<sup>4</sup> In a major STD clinic in New Delhi, the prevalence of HCMV IgM antibodies in STD clinic attendees was found to be 17% in females and 8.5% in males.<sup>43</sup>

### MODE OF TRANSMISSION

The virus may be present in milk, saliva, feces, urine, and genital fluids. Asymptomatic viral carriage in semen and cervical secretions is common.<sup>8</sup> The common mode of transmission of the virus is either through sexual route by exchange of semen, vaginal fluid or saliva, or nonsexual routes like respiratory, through blood transfusion, sharing needles, organ transplantation, and perinatal. Transfusion of whole blood or certain blood products containing viable leukocytes may transmit HCMV with a



frequency of 0.14–10% per unit transfused.<sup>8</sup> The infection can spread through secretions containing free virions or cell associated virus.<sup>11</sup> Contact with infected maternal genital secretions during delivery and breastfeeding<sup>3,8</sup> are the two main routes of perinatal infection. Children in day care centers and at school often infect each other through saliva. Congenitally infected infants have viruria for up to 4–5 years. They are highly infectious in early infancy. In spite of prolonged contact, the virus does not spread readily among adults by ordinary nonsexual mode of transmission, as evidenced by failure of transmission to healthcare workers (HCWs) even by close contact with infected patients,<sup>3</sup> although variable reports exist. However, infected children can transmit infection to HCWs.<sup>44</sup> Risk of acquiring HCMV infection is more in immunosuppressed persons. A high percentage (90%) of kidney and bone marrow recipients develop infection probably due to reactivation of their own latent virus. Almost all AIDS patients are seropositive for HCMV.

### Sexual Transmission of HCMV

Sexual transmission occurs in heterosexuals, men who have sex with men (MSM), and women who have sex with women. MSMs have the highest infection rate. The risk of acquiring infection increases with the number of sexual partners. Although condoms, if used properly, help to prevent sexual transmission, the virus can be transmitted through kissing.<sup>45</sup> The following evidences have been cited<sup>3</sup> to prove that HCMV is an STI: (i) HCMV can be isolated from semen and there is increase in seroprevalence with commencement of sexual activity; (ii) nonsexual transmission of HCMV in adults is infrequent, e.g., absence of seroconversion in HCWs and military recruits in close contact with infected persons; (iii) isolation of HCMV from cervix of 13–23% of women attending clinic for suspected STIs and a higher rate (10–12% per year) of seroconversion among seronegative women with multiple partners attending an STI clinic versus 1–2% per year in the general population. The seroconversion was associated with acquisition of other sexually transmitted pathogens like *Chlamydia trachomatis*. Demonstration of transmission of HCMV infection to the female sex partners of a man with virus positive semen during the preceding 5 months and infection of a man after sexual contact with a woman whose cervix and urine were HCMV positive, strongly indicate sexual transmission. The development of HCMV proctitis in a woman who had vigorous receptive anal intercourse for 4 consecutive days and the isolation of different strains of HCMV from the same sexually active adult<sup>46</sup> suggest that reinfection may occur in heterosexuals. In addition, there is a higher rate of urinary excretion of HCMV and antibody prevalence in homosexual men (7.4% and 93.5%, respectively) than in heterosexual men (0% and 54.3%, respectively). A high attack rate of 71% during a 9-month follow-up of seronegative homosexual men and at the same time development of viruria in 32% of the seropositive group suggest increased transmission risks in homosexuals. The widespread occurrence of viruria and viremia (5 times more than urine) accounts for the extraordinary high attack rate of HCMV

infections among seronegative homosexual men. Estimated mean duration of semen positivity was 22 months against 9 months for urine. The exposure of the anorectal mucosa to HCMV infected semen constitutes the major route of acquisition of infection by homosexual men.<sup>47</sup>

### Congenital HCMV Infection

In a review of published studies,<sup>48</sup> the overall birth prevalence of congenital HCMV infection was 0.64% but it varied considerably among different study populations. About 11% of live-born infants with congenital HCMV infection were symptomatic. Non-white race, low socioeconomic status, premature birth, and neonatal intensive care unit admittance were risk factors for congenital HCMV infection. Birth prevalence increased with maternal HCMV seroprevalence. The rate of transmission to infants born to mothers who had a primary infection or a recurrent infection during pregnancy was 32% and 1.4%, respectively.

### REINFECTION

Several studies in homosexual men indicated that multiple strains of HCMV can be acquired as well as excreted by homosexual men with and without HIV infection.

### MOLECULAR TYPING

Infection and reinfection with multiple HCMV strains occur in immunocompromised individuals, STD clinic attendees, and children attending day care centers. HCMV clinical isolates were distributed into 30 different strains using PCR-restriction fragment length polymorphism (RFLP) analysis of multiple viral subgenomic regions. The number of isolates is not uniformly distributed among strains.<sup>49</sup> It is possible to determine the source of infection in the family by molecular epidemiology, i.e., by comparing DNA sequences of HCMV strains.<sup>50</sup> HCMV PCR-positive specimens from seropositive women were analyzed for glycoprotein gN and gB genotypes by cloning, followed by nucleotide sequencing of the plasmid DNA and/or RFLP. The results showed that most (93.7%) of the PCR-positive specimens contained multiple gN and/or gB genomic variants, suggesting that the majority of women were infected with more than one virus strain. The results also showed that the RFLP technique might not be sufficiently sensitive to detect all of the genomic variants present in a sample.<sup>51</sup>

### Clinical Features

Once HCMV enters a person's body, it remains life long. In most healthy adults, infection becomes latent, meaning that the virus remains in the body and there is potential for reactivation and recurrent illness in immunosuppressed patients such as in post-transplant cases or in HIV infected patients. The extent and severity of HCMV disease depends on the patient population.



## CONGENITAL INFECTION

HCMV is the most common microbial agent to cause congenital infection. Survey of congenitally infected neonates<sup>3</sup> has shown that only 10% have 'cytomegalic inclusion disease,' whereas the rest are without obvious symptoms at the time of birth. The chances of acquiring congenital infection and the extent of disease in the newborn depend on the immune status of the mother (Box 33.1). In the US, approximately 1% of all neonates excrete HCMV, of which 10% will be severely affected with a wide range of symptoms.<sup>53–55</sup> In UK, 400 HCMV affected neonates are born annually.

Infants with cytomegalic inclusion disease show signs of intrauterine growth retardation, hepatosplenomegaly, and thrombocytopenic purpura (60–80%) and may have jaundice, microcephaly, or chorioretinitis. They may develop severe hearing loss, mental retardation,<sup>54,55</sup> and ocular abnormalities. Prognosis among severely infected infants is grave and mortality rate may range from 20% to 30%. Premature infants may present with poor weight gain, respiratory distress, rash, fever, and hepatosplenomegaly, occasionally associated with *Chlamydia trachomatis*, *Pneumocystis jiroveci*, or *Ureaplasma urealyticum* infections.<sup>8</sup> HCMV excretion often persists for months or years.

## PERINATAL INFECTION

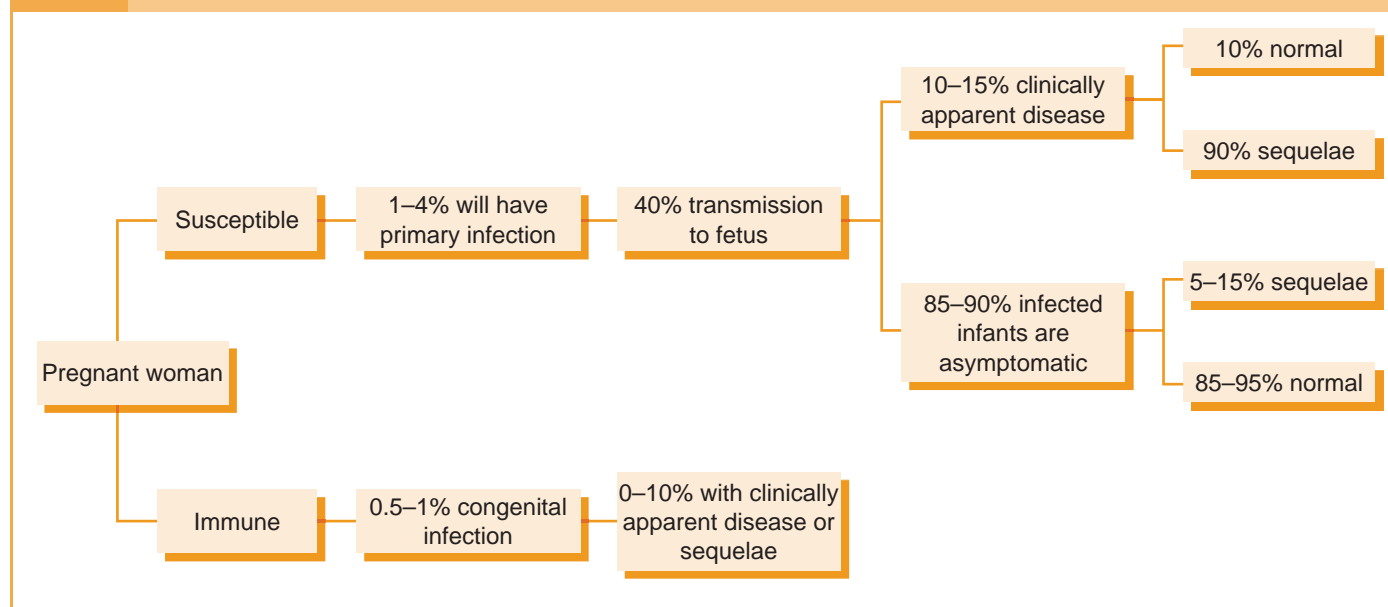
Full-term and otherwise healthy infants may acquire the infection during or shortly after birth by passage through infected birth canal or by postnatal contact with breast milk or other secretions, although they possess high titer of transplacentally acquired antibodies. Viral load in breast milk is an important factor for transmission of the virus.<sup>56</sup> These infants remain healthy but continue to shed the virus and sometimes develop learning

difficulties and deafness in childhood. Perinatal HCMV infection is also acquired through transfusion and there is even a low residual risk of HCMV transmission by both HCMV-seronegative and WBC-reduced seropositive blood.<sup>57</sup> In a recent study,<sup>58</sup> hepatosplenomegaly was the most common feature in these children. Other symptoms/signs were developmental delay, jaundice, convulsions, pneumonitis, visual and hearing impairment, hydrocephaly, congenital cataract, etc.

## INFECTION IN IMMUNOCOMPETENT ADULTS

Majority of children and adults experience a subclinical infection with HCMV marked only by seroconversion. Sexually active young adults are most often involved and the disease may also follow transfusion of blood products. Incubation period is 20–60 days and the disease generally lasts for 2–6 weeks. Intermittent shedding of virus from the pharynx, genital secretions, urine, or saliva may occur for many months or even years after primary infection. In those who develop clinical symptoms, a self-limited infectious mononucleosis like syndrome is the most frequent manifestation,<sup>59</sup> with few long term sequelae like prolonged fever, myalgia, malaise, and liver function abnormalities. These patients develop atypical lymphocytosis similar to infections with Epstein–Barr virus but without a positive heterophile antibody test. However, severe life-threatening complications of HCMV infection in immunocompetent patients may not be as rare as previously thought. In a recent review of available literature,<sup>60</sup> the gastrointestinal tract (colitis) and the central nervous system (meningitis, encephalitis, transverse myelitis) were found to be the most frequent sites of severe HCMV infection in these individuals. Manifestations from other organ-systems include hematological disorders (hemolytic anemia, thrombocytopenia), thrombosis of the venous or arterial vascular system, ocular

**Box 33.1** Perinatal Transmission of HCMV<sup>52</sup>



involvement (uveitis), and lung disease (pneumonitis). Recently, HCMV infection was found commonly in chronic HBV and HCV patients, who can be regarded as patients at high risk for HCMV disease. Replication of HBV and HCV were inhibited in HCMV-positive cases.<sup>61</sup> The virus has been observed in the female lower genital tract (cervix and vagina) with an incidence of 4% to 12%, as demonstrated by the presence of intracellular inclusion bodies on Papanicolaou smears or at direct biopsy.<sup>62</sup> Painful acute genital ulcers were reported in the context of a primary HCMV infection. HCMV disease should be considered in the screening of acute ulcers/swelling of the vulva.<sup>63,64</sup>

### INFECTION IN IMMUNOCOMPROMISED HOSTS

HCMV infection remains one of the most challenging infections in both solid organ transplant (and hemopoietic stem cell transplant recipients and is also responsible for life-threatening diseases in patients infected with HIV.<sup>65,66</sup> The spectrum of the disease varies, depending on the extent of immunosuppression. Retinitis, in subjects with HIV infection and pneumonia in recipients of transplants, are the main clinical manifestations. When immunosuppression is more severe, extensive overwhelming infections may result and patients may experience mild or severe hepatitis,<sup>66</sup> destructive retinitis, meningoencephalitis, poly radiculopathy, myelopathy, encephalitis, gastrointestinal tract disease, causing ulcers or bleeding, adrenal involvement, myocarditis, and pancreatitis.<sup>66</sup> The maximum period of risk appears from 1 to 4 months after transplantation, although retinitis may appear later. HCMV disease may occur in cancer patients.

### HCMV INFECTION IN AIDS PATIENTS

HCMV infection is extremely common in AIDS, causing retinitis or disseminated disease and may result in death.<sup>66</sup> The risk is directly related to severity of HIV disease, i.e., the degree of immunosuppression, which may be pronounced due to HCMV infection. Infection can be “new” or due to reactivation and severe and/or fatal organ involvement can occur. Retinitis is an important cause of blindness in these patients. Differential diagnosis from other causes of retinopathy, including toxoplasmosis, candidiasis, and HSV infection should be carried out.

## Laboratory Diagnosis

Testing for HCMV is usually not recommended as a part of routine STI screening because of the high rate of infection in the community and because HCMV in normal individuals does not cause much problem. Laboratory diagnosis is usually carried out when patients are having symptoms of suspected HCMV infection. Early diagnosis and the introduction of preemptive antiviral therapy have reduced HCMV-related mortality after allogeneic stem cell transplantation.

The virus is found in body fluids, including urine, saliva, breast milk, blood, tears, semen, and vaginal fluids. The diagnosis of primary symptomatic HCMV infection can be made only

by careful correlation of the clinical illness with the results of laboratory tests. It should be kept in mind that there is a high frequency of asymptomatic shedding of HCMV and appearance of IgM antibody during reactivation of latent virus.

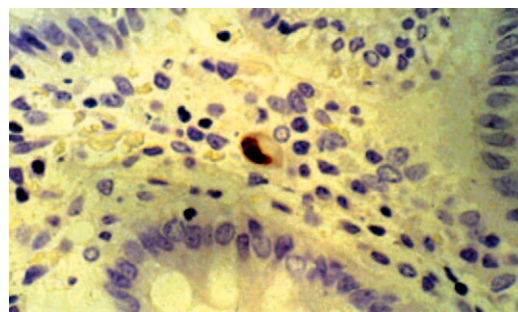
### DIRECT DETECTION METHODS

#### Direct Microscopy of Stained Smear/Tissues Under Papanicolaou/Hematoxylin-Eosin Stain

In cytological examination, HCMV infection cannot be implied unless typical HCMV-infected cells are present. Presence of large cells of 25–35  $\mu$  size containing massive central intranuclear, basophilic inclusion body, separated from nuclear membrane by a halo and resembling “owl’s eye,” is diagnostic (Fig. 33.2).<sup>67</sup> The small intracytoplasmic inclusions are visualized with Wright/Giemsa stain. However, such cells are not always observed in HCMV-infected cases. Sensitivity of the technique is less but it is rapid and more specific than culture.

#### Direct Detection of Antigen

HCMV antigen may be detected in histologic sections, blood collected in an anticoagulant (circulating neutrophils), and bronchoalveolar lavage fluids (BAL). In neonates, urine samples may be used for diagnosis in the first 2 weeks of life. A commercially available HCMV antigenemia assay was found to be a rapid and sensitive method<sup>68</sup> for evaluating transplant patients and HIV-HCMV coinfection. Monoclonal antibodies assist in the rapid diagnosis of HCMV infection in patient specimens as well as in cell culture. In lung biopsy specimens, the sensitivity is high. HCMV antigenemia assay is significantly more sensitive than shell vial cultures for detection of HCMV in the PMNL fraction of blood leukocytes and is recommended as the method of choice for rapid diagnosis of HCMV viremia,<sup>69</sup> specially in renal transplant patients.<sup>70</sup> However, any HCMV antigen assay may not be always useful in an immunosuppressed host as the antigenemia is transient and sensitivity varies from 31.6% to 100%.<sup>68,71</sup> Recently, it was observed that in bone marrow and liver



**Fig. 33.2:** Inclusion of cytomegalovirus in histologic section. *Courtesy:* SJ Wincelous, UK. Reproduced with permission from Schofield JB, Wincelous SJ. Anorectal manifestations of sexually transmitted infections. *Colorectal Dis* 2001;3:74–81.

transplant recipients, an immediate-early (IE) antigenemia assay could replace the pp65 antigenemia assay for early detection and monitoring of active HCMV infection.<sup>72</sup>

### Direct Detection of DNA

DNA and RNA hybridization, RNA amplification, cytohybridization, and polymerase chain reaction (PCR) assays for detection of HCMV DNA are more sensitive than culture and sensitivity is comparable with viral antigen detection techniques.<sup>73,74</sup>

- (i) Murex hybrid capture DNA assay (HCS) is a solution hybridization antibody capture assay for detection and quantitation of HCMV DNA in leukocytes. PCR is more sensitive than HCS, which is more sensitive than the blood culture assay. Although all patients with HCMV disease are correctly identified by HCS, the lower sensitivity limit of the HCS assay may still be insufficient to allow diagnosis of HCMV infection, early enough to prevent HCMV disease in patients.<sup>73</sup>
- (ii) PCR assay detects HCMV DNA in samples other than WBC, e.g., whole blood, plasma, BAL fluid, or cerebrospinal fluid.<sup>75</sup> PCR detection of HCMV DNA is a semiquantitative test and the quantity of HCMV DNAemia as well as pp65 antigenemia have correlated with risk and severity of HCMV disease in immunocompromised patients.<sup>76</sup> There is good association between double primer PCR assay of PMNL and antigenemia assays for detection of active HCMV infection in all patients of bone marrow transplants and the former can be an alternative method for antigenemia assay. Quantitative PCR methods are necessary for monitoring antiviral treatment.<sup>77</sup> Recently, high concordance between COBAS Amplicor HCMV Monitor (CACM) and an in-house PCR assay for the monitoring of HCMV infection was documented.<sup>78</sup>
- (iii) The real-time (RT) PCR assays, using TaqMan probes and molecular beacons to determine viral load in patients' samples compared well with a well-established, validated, gel-based PCR method and these are accurate, rapid, and reliable assays for the diagnosis and monitoring of EBV and HCMV infections.<sup>79</sup> In studies on AIDS patients undergoing liver and/or renal transplant, high peak viral load has been used for prediction of the development of active CMV diseases. With the availability of effective antiviral therapy, one goal of management is prevention of CMV disease through the detection of significant load of CMV DNA before end-organ disease has developed. Antiviral therapy can then be used to lower the CMV DNA levels and prevent the development of end-organ disease. RT PCR assay was found to be more useful than the direct immunoperoxidase (DIP) staining of leukocytes with peroxidase-labeled monoclonal antibody (C7-HRP test) as a rapid diagnostic test for early diagnosis and treatment of HCMV infection. RT PCR was useful for monitoring HCMV infection during treatment

using ganciclovir (GCV). Moreover, it was quicker, simpler, and cheaper than other RT PCR assays.<sup>80</sup>

Recently, the plasma RT-PCR from Abbott was found to be more suitable than the antigenemia assay for monitoring active HCMV infection in allogeneic hematopoietic stem cell transplantation (Allo-SCT) recipients and may be used for guiding preemptive therapy in this clinical setting.<sup>81</sup> The PCR assay tested positive both before the onset of symptoms and during the disease period.

- (iv) Quantitative-competitive DNA-PCR (QC-PCR) in peripheral blood was compared with HCMV pp65 antigenemia assay in leukocyte fraction, viremia, and the nucleic acid sequence-based amplification (NASBA) for detection of HCMV pp67-mRNA. Correlations of the number of pp65-positive cells with the number of HCMV DNA genome copies/mL and also with the pp67 mRNA-positivity were statistically significant.<sup>82</sup>

In HIV-infected patients, virological screening by qualitative assays from blood, urine, and throat swab specimens for detection of HCMV are of limited value for prediction of the development of HCMV disease.<sup>83</sup> A study carried out in AIDS patients proved by autopsy indicated that quantitative HCMV PCR is best used to rule in rather than to rule out HCMV disease in HIV-infected individuals at high risk.<sup>84</sup>

### ISOLATION OF VIRUS

The virus can be isolated from throat washings, urine, saliva, peripheral blood leukocytes, breast milk, biopsy material, infected liver, lung, semen, and cervical secretions.<sup>40</sup> It grows only in human diploid fibroblast cell culture<sup>85</sup> and usually requires 2–4 weeks. The time of development of CPE depends on the concentration of virus in the initial specimen. If the virus titers are high, as in congenital disseminated infection or in patients with AIDS, characteristic CPE may be detected within a few days. Rapid culture techniques have been developed and include:

- (i) **Detection of early antigen fluorescent foci (DEAFF) test** in cell culture is a rapid method of detecting HCMV. Inoculation of the specimens is carried out by centrifuging them in a shell vial with a cover slip, seeded with diploid fibroblast cells. After 16–36 hours of incubation, the cover slip is stained with either an immunofluorescence (IF) or immunoperoxidase (IP) labeled monoclonal antibody against the IE antigen. The DEAFF test and conventional cell culture had 99% concordance but the former gave much more rapid results<sup>86</sup> and is the current test of choice for the diagnosis of HCMV infection. A rapid assay for detection of HCMV in saliva compared well with standard culture, being as sensitive as detection of viruria. It was suitable for screening of newborns for HCMV as saliva can be collected with less difficulty and expense than urine.<sup>87</sup>
- (ii) **Culture amplified enzyme linked immunosorbent assay (EIA)** has also been used for rapid (within 24–



48 hours) detection of HCMV in the lung tissue of immunocompromised patients with life-threatening pneumonitis.<sup>88</sup> To prove the etiology of a suspected HCMV disease, it is important that tissue involvement is documented by the presence of inclusions, antigen, or viral nucleic acid within the cells, in addition to isolation of the virus.<sup>4</sup> Detection of HCMV viremia is a better predictor of acute infection.

## SEROLOGY

The serological tests (evidence of IgM activity, IgG avidity) for HCMV are useful in the immunocompetent host; whereas in the immunocompromised host, cytological detection (demonstration of typical cytological aspects and positive immunohistology for antigens) and/or virological detection (isolation of virus or evidence of viral antigens or viral DNA) are needed.

A battery of serological tests like complement fixation, IF, and EIA are available for detecting antibodies to HCMV.<sup>8</sup> However, rise in antibody level may not be detectable for up to 4 weeks after primary infection and titers may remain high for many years after infection. Therefore, a single serological assay is of limited value in the diagnosis of HCMV infection except in screening of blood or organ donors.

HCMV IgM may be detected during primary infection in infectious mononucleosis patients or in pregnant women but these tests may be nonspecific because of false-positivity. However, immunocompromised patients, having clinically significant HCMV infection, cannot mount an appropriate immune response and may acquire passive antibody due to frequent blood transfusions. Besides, homosexuals have high IgM levels because of repeated infections and reactivation.<sup>1</sup>

### Serological tests:

- (i) Immunoassays that use early antigen (recombinant HCMV CM<sub>2</sub> and p52) are 5 times more sensitive than HCMV EIA assay using viral lysate and are specific in the detection of active HCMV infection.<sup>89</sup>
- (ii) A luciferase immunoprecipitation system (LIPS) provides a highly robust and quantitative method for studying anti-HCMV antibodies and has the potential to document HCMV infection more accurately than standard EIA.<sup>90</sup>
- (iii) Different commercial assays, including Abbott AxSYM, for HCMV-specific IgM antibodies for the detection of recent HCMV infection, were compared. In selected IgM positive samples, an HCMV IgG avidity assay (Radim) and virus isolation from urine (shell vial) were also performed. There are differences in the sensitivity of the commercially available tests for HCMV antibodies.<sup>91</sup>
- (iv) Testing for IgG avidity antibody in pregnant women, positive for IgM antibodies, may increase the reliability of serological tests. An anti HCMV IgG avidity test was performed to exclude recent infection in patients with anti HCMV IgM antibodies, detected during the first trimester

and also on the follow-up, to exclude the risk of congenital infection. A high avidity index during the first trimester of pregnancy may be considered as a good indicator of past infection and invasive prenatal diagnosis is not necessary. Nearly 70% of the IgM-positive women may be reassured if the first serology is systematically performed before 12 weeks of gestation.<sup>92</sup> HCMV screening in pregnancy is performed as a first step by immunoassays and the choice of highly sensitive IgM tests, associated with further serological and virological methods, could help to identify early primary infections.<sup>93</sup>

- (v) A simple and reliable EIA, recently developed to detect antibodies against the polymorphic epitopes within the two envelope glycoproteins of HCMV, i.e., H and B, is useful for the detection of serologic responses to HCMV strains and the identification of HCMV reinfections.<sup>94</sup>

## Treatment

Asymptomatic HCMV patients do not need any treatment. For symptomatic patients, drugs like foscarnet, GCV, and VGCV are effective in treating the infection.<sup>102,103</sup>

### GANCICLOVIR

It is the most commonly used agent for the prevention of HCMV infection and disease in solid organ transplant recipients. It is a nucleoside analog, related to acyclovir but differs from it by a single carboxyl side chain. Because of this change, the drug is much more active than acyclovir against HCMV. The active compound produced in the body is ganciclovir triphosphate and it inhibits HCMV DNA polymerase. It is a virustatic agent, mostly used for serious HCMV disease like retinitis.

GCV is initially administered intravenously (IV) in a dose of 5 mg/kg twice daily for 2–3 weeks, followed by maintenance therapy of 5 mg/kg once daily to prevent or delay relapses. The recommended oral dose is 3 g daily but a higher dose may prove to be more effective, as oral ganciclovir is not absorbed well.<sup>104</sup> A sustained-release intravitreal implant of GCV is available.<sup>105</sup> A randomized study comparing the IV therapy with implant revealed much longer progression time in the group receiving the implant.<sup>106</sup> It has minimal systemic toxicity, while the other routes cause neutropenia, leading to premature discontinuation of treatment. The neutropenia is usually reversible and cytokines such as granulocyte colony stimulating factor help in reversal. GCV is especially toxic in patients on zidovudine. Sometimes it also causes nausea, vomiting, and diarrhea due to gastrointestinal (GI) disturbance and confusion, convulsions, headache and dizziness due to central nervous system (CNS) involvement. HCMV retinitis progresses in spite of active treatment but GCV slows the progression. It may also be useful in 70–90% of HCMV hepatitis and colitis but in only 30–50% of those with pneumonitis.



## GANCICLOVIR-RESISTANT HCMV

As a result of the widespread use of antiviral prophylaxis and preemptive therapy, there is increasing recognition of GCV-resistant HCMV infection. The overall incidence varies widely among transplant groups, with the highest incidence among recipients of lung and combined kidney–pancreas transplants.<sup>107</sup> Resistance has been reported due to impaired phosphorylation.

## FOSCARNET

It is an inorganic pyrophosphate analog and inhibits HCMV DNA polymerase without requiring intracellular phosphorylation as in the case of GCV. As mentioned previously, impaired phosphorylation is the mode of development of resistance to GCV and foscarnet may be used to treat patients with GCV-resistant HCMV strains. It is used as an alternative therapy for HCMV retinitis at a dose of 60 mg/kg IV, thrice daily for 2–3 weeks, followed by maintenance therapy of 120 mg/kg daily.<sup>107</sup> Efficacy of GCV and foscarnet in clinical trials has been found to be equivalent in treating retinitis.<sup>108</sup> A larger survival time was reported with foscarnet, probably because some of the patients were not able to tolerate concurrent GCV and anti-retroviral drugs because of increased myelosuppression. Moreover, foscarnet has intrinsic anti-retroviral activity. It is also useful in the treatment of HCMV GI disease. As excretion of foscarnet is entirely renal, it can cause renal toxicity, serum electrolyte imbalance, anemia, and neurotoxicity. Adequate hydration of patients with saline may reduce nephrotoxicity.<sup>8</sup> However, resistance to foscarnet can occur due to mutations in DNA polymerase. Combination of GCV and foscarnet is more effective in the treatment of refractory diseases.<sup>109</sup>

## CIDOFOVIR

It is active against majority of GCV-resistant viruses,<sup>110</sup> and may be administered at long intervals as maintenance dose, as it has got a long half-life. During therapy, the renal functions should be monitored, as the drug is nephrotoxic.

## VALGANCICLOVIR (VGCV)

It is an oral prodrug valyl derivative of GCV, with a 10-fold greater bioavailability than oral GCV. After absorption through the gut, the valine moiety is rapidly cleaved off by the liver, yielding GCV. The active drug is a guanosine analog that inhibits viral (and cellular) DNA synthesis by chain termination. Studies of VGCV among HIV-infected HCMV-seropositive patients and liver transplant recipients suggest that it has the potential to replace both oral and IV GCV in many situations.<sup>111</sup>

VGCV is administered orally and the recommended induction dosage is two tablets (800 mg) taken twice daily with food for 21 days; food increases bioavailability. The maintenance dosage is two tablets taken once daily with food. In liver-transplant patients and in patients with AIDS, this dosage gives maximum

serum concentrations and 24-hour total drug exposure equivalent to 5 mg/kg IV GCV twice daily and far greater concentrations than those achieved by the daily oral dosage of GCV. Because VGCV is excreted primarily through the kidneys, dosage must be decreased in patients with impaired renal function.<sup>112</sup> Oral VGCV is as effective as comparable doses of IV GCV in stopping progression of newly diagnosed HCMV retinitis.

Viruses resistant to GCV can be selected after prolonged treatment with VGCV. Initial resistance has also been noted in patients previously untreated with GCV. VGCV is highly effective for prophylaxis of HCMV reactivation in patients receiving alemtuzumab, an immunosuppressive antibody that destroys T and B cells.<sup>113</sup>

## Prevention

HCMV infection can be prevented in patients at high risk by screening of blood for HCMV antibodies before blood transfusion or organ transplantation and also using frozen thawed and deglycerolized blood. Component processing, leukocyte reduction, and platelet apheresis in normal blood and platelet donors reduce HCMV viral load quantified by PCR and were found to be effective in preventing transmission of HCMV infection.<sup>95</sup> Maintenance of strict hygiene, including hand washing and wearing of gloves while dealing with young children shedding HCMV, have been recommended.<sup>96</sup> In hospitals, standard precautions were found to be effective in preventing spread from infected patients to healthcare workers.<sup>97</sup> As HCMV in human breast milk poses risk to the premature infant,<sup>98</sup> milk from seropositive donors should not be provided to seronegative newborns. HCMV is commonly secreted in semen; therefore, HCMV antibodies should be screened in semen donors before artificial insemination.<sup>99</sup>

## CHEMOPROPHYLAXIS

Prophylactic acyclovir was found to reduce HCMV infections and disease in seronegative renal transplant recipients.<sup>8</sup> Alternate day ganciclovir/ foscarnet for HCMV prophylaxis in “at risk” allogeneic stem cell transplant related and unrelated recipients is 100% effective in preventing HCMV infections.<sup>100</sup> Oral valganciclovir (VGCV) facilitated treatment compliance without being inferior to other prophylactic therapies. However, it failed to provide adequate prophylaxis following liver transplantation.<sup>101</sup>

## HCMV VACCINE

Although several trials in humans are running at present, no successful vaccine is available to prevent HCMV infection. HCMV immunoglobulin prepared from sera of high titered donors has been reported to reduce HCMV associated syndromes and to prevent infections in renal and bone marrow transplant recipients but the results are not always favorable.

### Summary

Human cytomegaloviruses (HCMVs) are ubiquitous large DNA viruses grouped under herpes viruses producing a variety of human infections in all age groups. Like all herpes viruses, it establishes a lifelong latent infection once it enters a person's body, and there is potential for reactivation and recurrent illness in immune-suppressed patients such as in post transplant cases or in HIV infected patients.

The common mode of transmission of the virus is either through sexual route by exchange of semen, vaginal fluid or saliva, or nonsexual routes like respiratory, through blood transfusion, sharing needles, organ transplantation, and perinatal. Sexual transmission occurs in heterosexuals, men who have sex with men (MSM), and women who have sex with women.

Incubation period is 20–60 days, and the disease generally lasts for 2–6 weeks in majority of immune competent children and adults. It is a widespread opportunistic pathogen that causes no obvious clinical manifestation in healthy individuals, but poses an important public health problem because of the high frequency of congenital infections resulting in serious birth defects. Infections acquired after birth are generally mild and range from asymptomatic subclinical infection to a mononucleosis-like syndrome in normal individuals but may be fatal in immune-compromised patients. HCMV infection remains one of the most challenging infectious complications in both solid organ transplant and hemopoietic stem cell transplant recipients and is also responsible for life-threatening diseases in patients infected with HIV.

Testing is usually not recommended as a part of routine STI screening because of the high rate of infection in the community and because the virus does not cause much problem in normal individuals. Laboratory diagnostic procedures are usually carried out when patients are having symptoms of suspected HCMV infection, especially in allogeneic stem cell recipients. The diagnosis of primary symptomatic HCMV infection can be made only by careful correlation of the clinical illness with the results of laboratory tests. It should be kept in mind that there is a high frequency of asymptomatic shedding of virus and appearance of IgM antibody during reactivation of latent virus. Different direct detection methods are available like direct microscopy of stained smear/tissues to detect typical HCMV-infected cells, HCMV antigenemia assay, a rapid and sensitive method for evaluating transplant patients and HIV-HCMV coinfection, and different methods for direct detection of DNA. The virus can be isolated from throat washings, urine, saliva, peripheral blood leukocytes, breast milk, biopsy material, infected liver, lung, semen, and cervical secretions in human diploid fibroblast cell culture. In AIDS patients undergoing liver and/or renal transplant, high peak viral load has been used for prediction of the development of active HCMV diseases. The serological tests (evidence of IgM activity, IgG avidity) are useful only in the immune-competent host. However, rise in antibody level may not be detectable for up to 4 weeks after primary infection, and titers may remain high for many years after infection. Therefore, a single serological assay is of limited value in the diagnosis of this infection except in screening of blood or organ donors. A simple and reliable EIA, recently developed to detect antibodies against the polymorphic epitopes within the two envelope glycoproteins of HCMV, i.e., H and B, is useful for the detection of serologic responses to different strains and the identification of re-infection.

Asymptomatic patients do not need any treatment. For symptomatic patients, drugs like foscarnet, gancyclovir (GCV), and valgancyclovir are effective. Foscarnet may be used to treat patients with GCV-resistant HCMV strains.

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# Epstein–Barr Virus Infections

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# 34

## Introduction

The gamma herpes subfamily is characterized by their ability to establish latent infection of lymphocytes. By looking at gene structure and products, members of the family are further grouped into the *lymphocryptovirus* and *rhadinovirus* genera. Both these groups contain important pathogens implicated in acute and chronic human diseases and cause significant morbidity in immunocompromised individuals. In addition, these viruses are implicated in oncogenesis. The *rhadinovirus* group contains human herpes virus 8 (Kaposi sarcoma herpes virus KSHV). Epstein–Barr virus (EBV) is a member of the *lymphocryptovirus* group. Both these viruses may be transmitted sexually. This chapter will describe the biology and features of EBV disease pertinent to an adult STI/HIV or dermatology practice.

## Epidemiology

Infection with EBV is followed by the development of permanent EBV-specific antibody. Seroepidemiological studies of antibody to EBV show that detectable levels in the range of 90–95% are encountered in most populations from both developed and developing countries.<sup>1</sup> The majority of infections tend to occur in childhood, and over 50% of infections do occur by the age of 5 years. Infections early in life tend to be asymptomatic. With economic development, infections are increasingly seen in later life; however, even then, cases beyond the third decade of life are rarely seen.<sup>2,3</sup> When the infection is delayed to adolescence and adult life, the clinical syndrome of acute infectious mononucleosis (IM) occurs.

## Biology

EBV has two target tissues: (i) B-lymphocytes where infection is essentially non-productive and is the site of latency and (ii) stratified squamous epithelium such as that found in the pharynx and genital areas in which replication occurs. Primary infection typically occurs through the inoculation of EBV in infectious saliva (also known as “kissing disease”) onto stratified epithelium.

Transmission through the receipt of blood and other tissues has also been described.<sup>4</sup> Productive replication ensues with the infection of oropharyngeal mucosa. B-lymphocytes close to the site of infection become infected, and infection spreads via the circulation. Approximately one-third of adults develop the clinical syndrome of IM.

## LATENT INFECTION

EBV establishes latency within the B-lymphocytes. The DNA circularizes to form an episome.<sup>5</sup> Restricted gene expression allows the infected cell to evade immune surveillance. During latency, only one in 10 lymphocytes is infected. Clinical reactivation can recur but is an infrequent event in an immunocompetent individual. Subclinical reactivation and viral shedding do occur from both the genital and pharyngeal mucosal surfaces. Virus can be recovered from saliva in up to 20–33% of healthy individuals at any one time and in over 90% with follow-up over a year.<sup>6–8</sup> Rates are higher in the immunocompromised. Debate persists as to the origins of such reactivated virus. Recent data suggest that this virus results from re-infection of mucosa from reactivating virus in B-lymphocytes.<sup>9</sup> True chronic productive infection of the oropharyngeal mucosa has been described (oral hairy leukoplakia), but this is a relatively rare phenomenon and not seen in the immunocompetent.

## GENE EXPRESSION DURING DIFFERENT STAGES OF INFECTION

The infectious virus particle consists of a nucleocapsid containing double-stranded linear DNA. The viral genome of 172 kb has been fully characterized and is known to contain 90 genes. Infectious virions are produced during the lytic stage of the infection when a wide range of gene products can be detected.

During latency, 11 genes are differentially expressed: six gene codes for nuclear proteins (EBNA1–6), three codes for membrane proteins (LMP1, LMP2a, and LMP2b), and two codes for small RNA molecules, the EBV-encoded RNAs (EBERs). Of these, LMP1 and EBNA 1, 2, 3, 5, and 6 are essential for the transforming capacity of the virus. Patterns in the epidemiology

of EBV-related malignancies have been linked to differences in viral protein expression during latency.

### SEROLOGICAL CHANGES

A characteristic antibody response develops after primary infection with antibodies to viral capsid antigen (VCA) and the early antigens (EAs), followed in several weeks or months by antibodies to EBV nuclear antigen (EBNA).<sup>10</sup> The ability of EBV to maintain lifelong infection following primary infection with low levels of replication and viral shedding and enduring antigen exposure results in continued humoral immune response with lifelong antibodies to VCA and EBNA and low levels of antibodies to the EA complex that may only be intermittently detectable in 10–20% of individuals. Different serological markers and their interpretations are given in Table 34.1.

### STRAIN DIFFERENTIATION AND CO-INFECTION

EBV isolates can be categorized into two types, EBV-1 and EBV-2, based on gene polymorphism for EBNA2 (specifically EBNA2, 3A, 3B, and 3C).<sup>11–13</sup> EBV-1 and EBV-2 have biologic differences many of which are accounted for by differences in EBNA2. Type-1 and type-2 strains differ in their ability to transform B-lymphocytes in culture.<sup>14,15</sup> EBNA polymorphisms generate immunological responses that are both type-specific and cross-reactive. Responses to EBNA2 and 3A are partially cross-reactive between the two types. The antibody responses to EBNA3B and 3C are essentially type-specific.<sup>16,17</sup> Similarly, both cross-reactive and type-specific T-cell responses can be detected.

EBV-1 and EBV-2 are distributed widely geographically.<sup>18–20</sup> Infection with one type does not protect against subsequent infection by another type. Co-infection with EBV-1 and EBV-2 is reported in 9–27% of populations and appears to be higher in STI clinic attendees. In addition, distinct subvirus populations have been identified from separate anatomical sites in patients suggesting that oral and genital exposures may result in different infections. Neither EBV type shows anatomical site specificity.

### CLINICAL FEATURES

Primary EBV infection may be seen as a benign lymphoproliferative disorder. The characteristic features are the gradual onsets of sore

**Table 34.2:** Clinical Signs/Symptoms and Laboratory Investigations in Infectious Mononucleosis

Clinical sign/symptom	Percentage
Lymphadenopathy	97
Pharyngotonsillitis	77
Fever	81
Splenomegaly	56
Hepatomegaly	13
Jaundice	7
Myocarditis	3
Meningoencephalitis	<1
Genital ulcers	<1
Laboratory test	Percentage
Elevated transaminases (>40 IU)	85
Neutropenia (<3000 cells/ $\mu$ L)	70
Lymphocytosis (>50% lymphocytes)	70
Thrombocytopenia	20
Hemolytic anemia	4

throat, fever, and lymphadenopathy. Diagnostic clinical and laboratory criteria are given in Table 34.2. This disseminated infection can involve almost any system. Most symptoms resolve within 4 weeks.<sup>21</sup>

Occasionally, IM may be confused with symptomatic primary HIV-1 infection. However, the presence of hepatosplenomegaly and heterophil antibody is a useful differentiating point. However, it is advisable that when HIV does enter the differential diagnosis, the laboratory confirmation of EBV infection is a must. If tests for EBV such as heterophil and VCA immunoglobulin M (IgM) antibody tests are negative, then tests for early HIV infection should be conducted (HIV RNA reverse transcriptase-polymerase chain reaction or proviral DNA detection with HIV p24 antigen tests).<sup>22</sup>

Young children rarely develop symptoms. Symptoms, if present, are similar to those found in adults although pharyngitis and lymphadenopathy tend to predominate.

Serious fatal complications are rare and estimated to be less than one case per 3000.<sup>21</sup> Deaths occur predominantly in patients with immunodeficiency who present atypically. Severe tonsillar enlargement resulting in respiratory obstruction, pneumonitis, splenic rupture, neurological involvement, liver failure, and myocarditis have been described in previous studies.<sup>23</sup>

Patients, if admitted to hospital with IM, do not require isolation conditions.

### Diagnosis and Management of Primary EBV Infection

The heterophil (Paul-Bunnell) antibody test is positive in most (>90%) of patients over the age of 10 with IM.<sup>24</sup> However, in younger children it is unreliable and it is then necessary to perform specific EBV serology.

Much is now known concerning the immunopathology of IM. The severity of acute symptoms in IM is related to the extent of immune activation and is predominantly mediated by this

**Table 34.1:** Interpretation of Epstein–Barr Virus Serology Test Results

Clinical situation	Heterophile antibody	IgG-VCA	IgM-VCA	EA	EBNA
No past infection	Usually –	–	–	–	–
Acute infection	Usually +	+	+	+	–
Convalescent phase	+/-	+	+ or –	+ or –	+
Past infection	Usually –	+	–	– or W+	+
Chronic or reactivation	Not useful	+	–	+	+

EA, early antigen; EBNA, Epstein–Barr nuclear antigen; VCA, viral capsid antigen; W+, weakly positive.

mechanism.<sup>22</sup> Symptoms appear to be associated with an excessive burst of cytokines induced by virus-mediated polyclonal B-cell activation resulting in immunogenic B-lymphocytes. Patients lacking both EBV-induced IFN- $\gamma$  and perforin-positive, CD8-positive T-cells have generally been found to develop disseminated infection proceeding to long-lasting lymphoproliferative disorders. In the usual situation, the development of the CD8-positive T-cell immune response is followed by the rapid decline in number of EBV-infected B-cells, going from 1–30% at the height of IM to less than 0.0002%.<sup>25</sup>

### Treatment of Infectious Mononucleosis

Numerous trials of antivirals and immune modulators have been conducted. Generally, the use of antivirals has demonstrated no significant effect on IM-associated symptoms despite good evidence of significant antiviral effects.<sup>26–28</sup> This is not surprising since most of the symptoms of IM are considered to be due to immune mechanisms and not the direct consequence of viral replication.

However, despite these findings it is still advisable to treat EBV-related life-threatening complications including autoimmune thrombocytopenia, hemolytic anemia, fulminant hepatitis and meningoencephalitis with convulsions.<sup>22</sup>

Although trials of steroids with antivirals have shown no reduction in signs or symptoms related to IM, they may still be indicated in some situations. Steroids may be helpful in reducing swelling and reducing obstructive symptoms and are helpful in managing thrombocytopenia.<sup>27</sup> Intravenous IgG has also been used in thrombocytopenia and shows a much more rapid effect.<sup>29</sup> Plasmapheresis combined with pooled human IgG has also been shown to be effective in cholestatic hepatitis, thrombocytopenia, and disseminated intravascular coagulation.

Interstitial pneumonitis complicating IM may be treated with a combination of subcutaneous IFN- $\gamma$  with oral steroids and acyclovir. Low-dose serotonin blockade (citalopram) has been used in post-infectious asthenia and in open studies shows a 50% response.<sup>30</sup>

### Primary EBV Infection in the Immunocompromised State

Patients with acquired or congenital immunodeficiency may develop hemophagocytic syndrome, agammaglobulinemia, aplastic anemia, or lymphoma after IM.<sup>31,32</sup> In these cases, serological markers of EBV may be lacking, and the diagnosis has to be based on EBV DNA detection by PCR.

Fatal IM has been described in familial clusters occurring in boys inheriting this susceptibility in an X-linked pattern.<sup>33,34</sup> The syndrome is characterized by the persistence of IM-like symptoms that eventually develop into aplastic anemia, lymphoproliferative disorder, or lymphoma. It is fatal in 75% of the cases. Once diagnosed in a family, prophylactic antivirals with bone marrow transplant of other susceptible members can be completely protective.<sup>35</sup>

### Genital EBV Infection

Many lines of evidence indicate that genital epithelium can be infected by EBV and subsequently can shed EBV intermittently. The B-lymphocyte receptor for EBV, C3d, has been found on genital epithelial cells.<sup>36</sup> Cell-free EBV can be detected in cervical washings, and EBV DNA can be detected by in-situ cytohybridization. PCR has detected EBV DNA in uterine cervix, urethra, vulva, and anal mucosa. EBV can also be found in infected discharges.<sup>37–42</sup> It is however, unknown as to whether genital EBV is primarily contracted sexually and as to whether genital EBV is infectious to partners.

An important issue has been to investigate if the presence of genital EBV could be related to specific micromorphological patterns in the genital epithelium. In a study, EBV was demonstrated to be present in 47% of women with acetowhite koilocytotic lesions of the vulva compared to 11% of the controls.<sup>40</sup> However, care needs to be exercised in the interpretation of results such as these. Acetowhite changes are non-specific<sup>43</sup> and may indicate an area of inflammatory change where B-lymphocytes carrying EBV are especially found. Future studies using in-situ hybridization may resolve this issue.

There are a number of reports in the literature concerning genitals ulcers in patients with IM.<sup>44–47</sup> These cases document the development of acute labial ulcers associated with symptoms and signs of classical IM. Ulcers tend to be deep and characteristically have purple–blue edges. It is highly likely that these lesions are under-reported, and EBV should enter the differential diagnosis of new genital ulcers especially if other more common causes have been excluded.

### EBV Infection in Pregnancy

Symptomatic congenital EBV infection is rare and most likely influenced by the low proportion of women of childbearing age who are susceptible to primary EBV infection during pregnancy and the low pathogenicity of EBV for fetal infection.<sup>48–53</sup> Cases of IM in pregnancy have been reported and followed prospectively showing little apparent risk of fetal involvement. A few cases have been reported with adverse fetal outcome—however, these reports do not conclusively corroborate EBV as the cause of these anomalies.<sup>54–57</sup> Very rare cases of symptomatic congenital EBV have been virologically confirmed, but there is no specific pattern of malformations.<sup>58</sup> The likelihood following either primary or reactivated EBV infection during pregnancy is for a normal outcome.

### EBV INFECTION IN THE IMMUNOCOMPROMISED STATE

The immunocompromised state disrupts the balance between host and EBV. There is an increased risk of reactivation and re-infection with a co-infecting strain. Lack of immune control results in elevated levels of EBV both in peripheral sites as well as the blood.<sup>59–61</sup> Some episodes of reactivation may be associated



with clinical symptoms. Seroepidemiological studies show that most EBV-related malignancies are preceded by a period of enhanced viral activity.<sup>62–64</sup> That such conditions are seen in such high frequency among the immunocompromised may be a consequence of the high burden of EBV that these patients carry.

A number of conditions have now been linked to EBV in the immunocompromised host: polyclonal B-cell proliferation, opportunistic lymphoma, necrotizing hepatitis, uveitis, bronchiolitis obliterans, genital ulcers, and hairy leukoplakia.<sup>65,66</sup>

EBV or part of the EBV genome has also been detected in a variety of neoplastic diseases including African Burkitt lymphoma, nasopharyngeal carcinoma, gastric carcinoma, and leiomyosarcoma.<sup>67</sup> It still remains to be seen whether EBV is a direct cofactor in the genesis of these tumors or an innocent passenger in activated proliferative cells.

### ORAL HAIRY LEUKOPLAKIA

Oral hairy leukoplakia is the only known pathologic manifestation of replicative EBV infection.<sup>68</sup> It is due to EBV-induced cellular proliferation in mucocutaneous cells. It occurs in up to a quarter of HIV-positive homosexual men with AIDS and is also seen in other states of advanced immunosuppression. Rarely it has been reported in healthy individuals.<sup>68,69</sup>

Lesions appear as well-demarcated keratotic areas with a “hairy” or corrugated appearance. Lesions are usually only a few millimeters in size but can be extensive involving large areas of the lingual and oral surfaces. Histological examination will show thickening of the epithelium with characteristic balloon cells resembling koilocytes. Hyperkeratosis results in microscopic hair-like projections on the surface. Viral particles can be seen on electron microscopy. These lesions are rarely symptomatic, although a variety of symptoms have been described including pain. Malignant transformation has not been described, and lesions will usually regress if the underlying immunosuppression can be improved. Lesions do respond to acyclovir therapy.

### EBV-Associated Malignancies in AIDS

A number of malignancies that are related to EBV are seen in significantly higher frequency in the AIDS population. Non-Hodgkin lymphoma (NHL) is 60 times more common in AIDS.<sup>70</sup> NHL can be morphologically divided into Burkitt-like and immunoblastic lymphomas, both of which have a higher association with EBV in AIDS than in the non-AIDS population.<sup>65,66,71</sup> EBV-1 and EBV-2 are both equally associated, reflecting the high prevalence of both these viruses within the HIV population. Burkitt lymphoma appears early in the course of AIDS and is usually not associated with profound immunosuppression. Immunoblastic lymphomas are seen much later in the disease course and usually when cellular immunity is severely disrupted. Immunoblastic lymphomas express latent viral proteins LMP1 and EBNA2 that would normally provide adequate targets for immune control via EBV-specific cytotoxic T-cells.

Within the general population, the association of Hodgkin disease with EBV depends upon the exact histological types. Mixed cellularity and lymphocyte-depleted subtypes are most closely related to EBV, and it is these types that are most often seen in AIDS. Up to 90% of AIDS-related Hodgkin disease is EBV related.<sup>72,73</sup>

Some malignancies not associated with EBV within the general population are found to consistently contain EBV within the HIV-positive population. Both leiomyosarcoma and primary central nervous lymphoma have been shown by in-situ hybridization to contain EBV in AIDS patients.<sup>74</sup>

Using low-dose hydroxy urea has shown to be effective in three patients with EBV-associated primary central nervous system lymphoma in a study.<sup>75</sup> Cidofovir, the acyclic nucleoside phosphonate analog, has shown an antitumor effect against EBV-transformed epithelial cells and lymphocytes in animal studies.<sup>76</sup>

### Future Developments

Significance of EBV-related malignancies has led to considerable efforts to develop effective prophylactic and therapeutic vaccines. Subunit vaccines are actively being explored.

#### Summary

Discovered in 1964, the Epstein–Barr virus (EBV) is widespread in all regions of the world infecting over 95% of the adult population. After initial exposure, EBV establishes a latent infection that persists for the life of the host. It was shown to be the causal agent of infectious mononucleosis in 1970 and since then has been linked to several other clinical syndromes. EBV has been implicated as an etiologic agent in Burkitt lymphoma, post-transplant lymphoproliferative disorders and lymphoma in HIV-infected individuals. Despite obvious epidemiologic implications of a genital distribution of EBV, evidence for direct sexual transmission is lacking. EBV targeted therapies for EBV-positive tumors have shown promise in certain patient groups. Prophylactic and therapeutic vaccines are under evaluation.

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# Kaposi Sarcoma Herpesvirus

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## Introduction

Kaposi sarcoma-associated herpesvirus (KSHV), which is also known as human herpesvirus 8 (HHV-8), is an oncogenic gammaherpesvirus that is the etiological agent of Kaposi sarcoma (KS), a mesenchymal tumor characterized by *de novo* vascular formation and lymphocyte infiltration. KSHV is also involved in the pathogenesis of two lymphoproliferative disorders, primary effusion lymphoma (PEL) and multicentric Castleman disease (MCD). As early as the 1960s, the uneven geographical distribution led to the speculation that KS was caused by an infectious agent.<sup>1</sup> This suspicion was compounded by the dramatic rise in KS incidence among immunosuppressed individuals (acquired or iatrogenic) in the 1980s.<sup>2</sup> Moreover, the very high prevalence of KS among people with acquired immune deficiency syndrome (AIDS) pointed towards a sexually-transmitted agent. KS occurs predominantly among homosexual men with human immunodeficiency virus (HIV), with a lower incidence in those who acquired HIV through heterosexual contact and a still lower incidence among those with parenterally-acquired HIV, for example, intravenous drug users and hemophiliacs.<sup>3</sup>

In 1994, Chang et al. identified novel herpesvirus DNA sequences from KS lesions in AIDS patients.<sup>4</sup> Molecular and serological epidemiology studies confirmed that this new herpesvirus (the eighth to be discovered, hence human herpesvirus 8) was present in individuals with all forms of KS, but was not ubiquitous in the general population.<sup>5-7</sup> Furthermore, high levels of HHV8 DNA in the peripheral blood of AIDS patients predicted subsequent development of KS.<sup>8,9</sup> PCR *in situ* hybridization showed that HHV8 was present in endothelial cells and spindle (tumor) cells of KS lesions from all epidemiological forms of KS,<sup>10</sup> and so the virus rapidly became known as KS-associated herpesvirus (KSHV). The observation that KSHV is latently expressed in more than 90% of tumor cells in advanced KS lesions<sup>11</sup> provided further evidence that KSHV was indeed causally-related to KS.

## Molecular Virology of KSHV

KSHV belongs to the lymphotropic herpesvirus subfamily, *gammaherpesviridae*. It is most closely related to the human gamma-1 herpesvirus, Epstein-Barr virus (EBV) or human herpesvirus 4 (HHV4). Like EBV, KSHV establishes latent infection in B cells.<sup>12</sup> However, it has an unusually wide cellular tropism, and has been detected *in vivo* in endothelial cells,<sup>10</sup> epithelial cells,<sup>13</sup> macrophages, and monocytes.<sup>14</sup>

KSHV is a large double-stranded DNA virus. The KSHV genome is approximately 165kb long, with a continuous 145kb-long unique coding region flanked by multiple GC-rich terminal repeat units approximately 800bp in length.<sup>15</sup> Over 90 open reading frames (ORFs) have been identified within the KSHV genome, of which at least 81 ORFs are over 100 amino acids long. The genome consists of seven highly-conserved gene blocks separated by short regions of unique or subfamily-specific genes. The conserved genes have homologs among other herpesviruses and include genes that code for structural proteins and genes involved in viral DNA replication and regulation of gene expression. A large number of the viral genes (both conserved and unique) encode homologs of cellular genes that have been captured from the host during the course of the virus's evolution.<sup>16</sup>

KSHV has developed several complex strategies for subverting the host's adaptive and innate immune system. Approximately one quarter of KSHV genes—both cellular homologs and unique viral genes—are involved in immune evasion. The roles of many viral genes in driving oncogenesis have also now been elucidated and, in many cases, these oncogenic activities result from the same molecular pathways employed by the virus in its immune-evasion activities.<sup>17</sup> The list of cellular processes modulated by KSHV viral genes includes the cell cycle, apoptosis, cytokine production, antigen presentation, cell signaling, and signal transduction. Thus, KSHV infection can result in aberrant cell growth, proliferation, inflammation, and angiogenesis, all of which contribute towards tumor development.

The KSHV ORFs are differentially expressed during the course of the virus's life cycle. During latent infection, the virus exists in



the nucleus as a closed circular episome and very few viral genes are expressed. During the lytic phase of the virus's life cycle, which is the replication phase, the virus linearises and most viral genes are expressed in a temporally-regulated fashion.<sup>18,19</sup> The constitutively-expressed latent genes and lytically-induced genes are referred to as class I and class III transcription units, respectively. Genes displaying a third pattern of gene expression, designated class II transcription, are expressed at low levels during latency but are also induced during lytic replication. Lytic genes are induced sequentially and can be further classified as immediate-early, early or late genes based on the timing of their appearance during replication. The chronological expression of lytic genes correlates with their function. Genes involved in transcription regulation are induced first, followed by those involved in DNA replication and repair, and genes that are involved in virus assembly or code for structural proteins are induced last. Viral homologs of cellular genes involved in immune evasion are predominately immediate-early or early genes, in keeping with their function to prevent the virus from attracting immune surveillance as it replicates in preparation for shedding of virions.<sup>20</sup>

Latent infection itself is, arguably, the primary strategy in immune evasion, as the highly-restricted pattern of viral gene expression that defines latency minimizes the number of viral epitopes that are presented by infected cells to the circulating cells of the immune system. Latency is also the state assumed to lead to clonal proliferation of KSHV-infected cells, since lytic replication results in cell death and is therefore anti-tumorigenic (as the host cell is lysed to release active virions). The vast majority of tumor cells in KS and PEL are latently infected, with only a few cells undergoing lytic replication. Tumor cells from MCD, by contrast, express both latent and lytic proteins.<sup>21,22</sup> Although latent infection is a characteristic of all herpesviruses, the latency genes themselves are not conserved between members of the family, but rather are highly evolved to adapt to their specific host cell environment. The function of the better described genes of KSHV is shown in Table 35.1.

**Table 35.1:** Table of the Better Characterized KSHV Genes

KSHV ORF	Gene product	Function(s)
<b>Latent</b>		
ORF 71	vFLIP	Antiapoptotic
ORF 72	vCyclin	Homolog of cellular cyclin D
ORF 73	LANA-1	Maintenance of the episome, gene expression Immune evasion—inhibition of antigen presentation
<b>Expressed at low-levels in latency and induced during lytic cycle</b>		
K11.1	vIRF-2	Immune evasion—disruption of host antiviral interferon response
K12	Kaposin	Oncogenic, promotes cell proliferation
K15-P	LAMP	Immune evasion—down regulates B-cell receptor signal transduction Activates NFκB, ERK2, and JNK1 pathways
<b>Immediate-early</b>		
ORF 50	Rta	Gene expression—transactivator of lytic replication; both necessary and sufficient for lytic cycle induction

KSHV ORF	Gene product	Function(s)
K8	Zta or K-bZIP	Gene expression—transactivation
ORF 57	KS-SM	Gene expression—post-transcriptional regulation
ORF 9		DNA replication—viral DNA polymerase
ORF 6	SSB	DNA replication—single strand DNA binding protein
ORF 16	vBcl-2	Antiapoptotic—inhibits BAX-mediated and virus-induced apoptosis
K7	vIAP	Antiapoptotic—protects against apoptosis induced by various stimuli
K2	vIL-6	Binds gp130 directly to activate the JAK/STAT signaling pathway Antiapoptotic—inhibits IFN-mediated apoptosis Immune evasion—inhibition of chemokine-driven recruitment of neutrophils
K6	vCCL-1	Immune evasion—skewing of CD4+ T cell response to Th2-type (less effective against intracellular pathogens)
K4	vCCL-2	
K5	MIR2	Immune evasion—downregulates expression of MHC-I, CD86, ICAM1, PECAM1, and CD1d
K14	vCD200 or vOX2	Immune evasion—inhibits myeloid cell activation, reduces production of Th1-attracting cytokines, inhibits neutrophil function
ORF 45		Immune evasion—disruption of host antiviral interferon response by interfering with IRF-7 activity
ORF 74	vGPCR	Binds IL-8; constitutively active GPCR
ORF 58		
Early		
ORF 59	PF8 or PPF	DNA replication—processivity factor, needed for efficient extension by the viral DNA polymerase
ORF 61		DNA replication—large ribonucleotide reductase
K4.1	vCCL-3	Immune evasion—skewing of CD4+ T cell response to Th2-type
K3	MIR1	Immune evasion—downregulates expression of MHC-I and CD1d
K9	vIRF-1	Immune evasion—disruption of host antiviral interferon response; downregulates MHC-I
ORF 4	CBP or KCP	Immune evasion—inhibition of complement
ORF 49		Activates the JNK and p38 MAP kinase pathways
ORF 8	gB	Structural—glycoprotein B
ORF 65		Structural—capsid-interacting protein
Late		
K1		Immune evasion—downregulates B-cell receptor surface expression
ORF 28		
ORF 33		
ORF 36		Activates the c-Jun N-terminal kinase (JNK) pathway
ORF 37	SOX	Immune evasion—host mRNA shut off
K8.1	gp35/37	Structural—glycoprotein 35/37
ORF 22	gH	Structural—glycoprotein H
ORF 25		Structural—major capsid protein
ORF 26		Structural—minor capsid protein

## Epidemiology and Transmission

A serological study by Gao et al. found no evidence of KSHV infection in healthy US blood donors, whereas they observed intermediate to high seroprevalence of KSHV among control populations from Italy (4%) and Uganda (51%)—two countries where KS is endemic.<sup>5</sup> Lennette et al. reported a similar pattern of KSHV seroprevalence, with dramatically higher incidence in the general population of Africa compared to the US, although the actual rates they observed were much higher than the previous study (80% in Uganda and between 4% and 28% in the US depending on the age of the individual).<sup>23</sup> These, and further studies into the epidemiology of KSHV infection, revealed that KSHV is a necessary but not sufficient factor in KS pathogenesis, with immunosuppression representing another important cofactor.

The exact mode of transmission of KSHV is not known. In the West, evidence points towards sexual transmission, with homosexual men having the highest risk of contracting the virus.<sup>24</sup> KSHV has been detected in semen<sup>25</sup> and risk of infection correlates with the number of sexual partners.<sup>26</sup> However, the route of conduction between sexual partners is not known. An extensive study by Dukers et al. into the risk factors for contraction of KSHV among homosexual men found that orogenital sex was significantly associated with KSHV seroconversion, and that this practice was more important than the number of sexual partners.<sup>27</sup> KSHV DNA is readily detectable in saliva and nasal secretions, and cell-free saliva fluid has been demonstrated to infect cell lines *in vitro*.<sup>28–30</sup> Together, this implicates the oropharynx as a possible site of KSHV replication and indicates a role for saliva in KSHV transmission. This is in keeping with the mode of transmission of Epstein-Barr virus, the most-closely related human herpesvirus to KSHV,<sup>31</sup> but has not been definitively confirmed.

By contrast, within African populations seroepidemiological studies point towards horizontal, nonsexual transmission of KSHV, with seroconversion frequently occurring before puberty and seroprevalence increasing linearly with age.<sup>32–36</sup> As with transmission between sexual partners, oral routes of transmission have been suggested and would explain both mother-to-child and sibling-to-sibling transmission. Alternatively, high mother-to-child transmission rates<sup>37</sup> could indicate a role for breast milk, although there is as yet no evidence to support this.

## Kaposi Sarcoma

KS is named after Moritz Kaposi, an Austro-Hungarian dermatologist who first described the disease. In 1872, Kaposi published the case histories of 5 patients suffering from what he described as “idiopathic multiple pigmented sarcomas” of the skin. This form of the disease is now known as “Classic KS”. It is a relatively indolent disease, often confined to the extremities. It is generally a chronic condition persisting for several years before unrelated fatality. Classic KS is predominant in elderly patients, more frequently men, of Mediterranean, Eastern European, or Middle Eastern origin.<sup>38</sup>

A second form of KS, known as “Endemic KS”, was prevalent in Africa predating the emergence of HIV.<sup>39</sup> It is a much more aggressive form of the disease, often spreading to the lymph nodes and affecting both adults and children.<sup>40</sup> Retrospective examination of medical records from the 1960s indicated that endemic KS accounted for between 4.5% and 7.0% of tumors seen in Ugandan men.<sup>41,42</sup> However, until the 1980s, KS (endemic or classic) remained a relatively rare neoplasm, particularly in North America and Western Europe, where it was almost unseen.

In 1981 an unusual epidemic of KS cases in young men from New York City and San Francisco was one of the first signs of the outbreak of AIDS.<sup>43</sup> This new form of KS, dubbed AIDS-KS, became an AIDS-defining disease and remains the most frequent malignancy in people living with HIV.<sup>44</sup> Since the advent of highly-active antiretroviral therapy (HAART), KS incidence has declined substantially among those with access to these medicines.<sup>45,46</sup> However, AIDS-KS remains one of the most common cancers across Africa, with KS recently estimated to account for 12.9% of all cancers in African males and 5.1% of all cancers in African females.<sup>47</sup> AIDS-KS is an aggressive disease, often affecting the mouth, lungs, gastrointestinal tract, or genitalia.<sup>44</sup>

The 1980s also saw the rise of a fourth epidemiological variety of KS. ‘Iatrogenic KS’ occurs in allograft transplant recipients, and other patients receiving immunosuppressive therapy. KS is up to 150 times more common in transplant recipients than the general Western population. Interestingly, transplant recipients in the West with origins (first or second generation) in countries where classic or endemic KS is prevalent are at greater risk of developing iatrogenic KS. This suggests an increased risk of developing KS among these populations even after geographical relocation,<sup>48</sup> which is likely to be simply explained by a higher prevalence of KSHV infection. There is, however, evidence that iatrogenic KS can arise from both reactivation of pre-transplant KSHV infection and by primary infection through receipt of a KSHV-infected graft.<sup>49,50</sup>

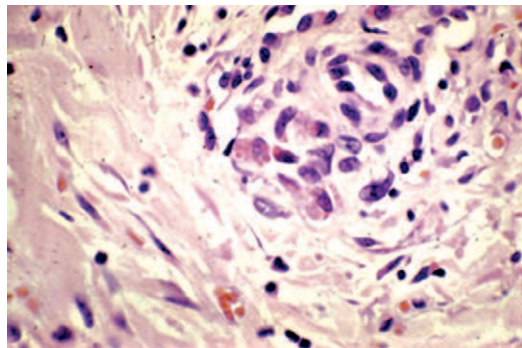
## PATHOLOGY

KS is a complex tumor with three distinct phases referred to as patch, plaque, and nodular grades. Lesions are usually multi-focal, and can arise in the skin, viscera, or mucosa.<sup>38</sup> The KS tumor cell is considered to be the spindle cell, which is distinguished by its spindle-shaped morphology and dominates final-stage nodular lesions.<sup>51</sup> The exact origin of the spindle cell is unclear although recent immunophenotyping and gene expression microarray evidence points towards a lymphatic endothelial origin. Further studies demonstrated that *in vitro* infection of blood endothelial cells with KSHV leads to lymphatic reprogramming of these cells and so it has been suggested that *in vivo*, blood vessel endothelial cells are converted towards a lymphatic phenotype by latent KSHV infection, giving rise to the spindle cell.<sup>51</sup>

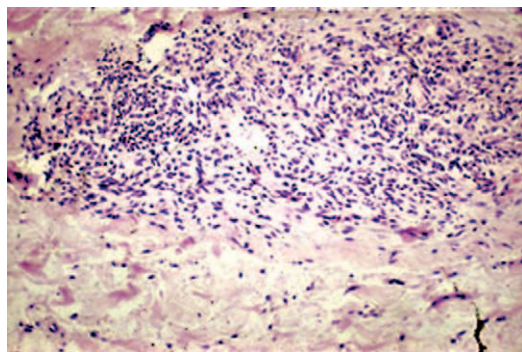
Despite their different clinical manifestations, KS lesions observed in the four epidemiological forms of KS outlined above are histologically indistinguishable at comparative stages. At the earliest stage, the patch stage, KS lesions are macular and



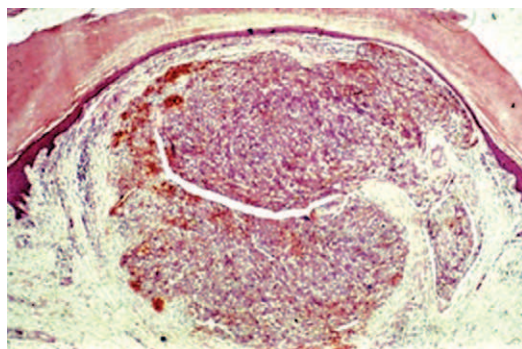
characterized by a proliferation of small, irregular endothelial lined spaces surrounding normal dermal blood vessels with an accompanying infiltration of inflammatory lymphocytes (Fig. 35.1a). At the plaque stage, the lesions become palpable, and the abnormal vasculature spreads through the entire dermis and sometimes into the subcutaneous fat (Fig. 35.1b). Clusters of spindle cells expand around the vascular spaces, and varying numbers of erythrocytes fill the channels. Nodular-stage KS lesions develop areas of pigmentation and are composed of sheets and large fascicles of uniform spindle cells, some of which are undergoing mitosis (Fig. 35.1c). Erythrocytes are trapped within



\*c+



\*d+



\*e+

**Fig. 35.1:** Histological stages of Kaposi sarcoma. (a) Early Kaposi sarcoma patch stage with small vessels with hyaline bodies within cells. (b) Plaque stage Kaposi sarcoma with presence of ill-defined spindle cell proliferation forming small vascular spaces and associated with a mild chronic inflammatory cell infiltrate including plasma cells. (c) Nodular Kaposi sarcoma.

an extensive network of slit-like vascular channels. The channels themselves, however, are not well-defined, lacking pericytes in their walls and with fragmentation of their endothelial lining and basal lamina.

An unusual feature of KS tumor biology is the important role played by inflammatory infiltrates, particularly at KS onset. The development of KS may thus be seen as a multi-factorial process in which infection by KSHV is a requirement; immunosuppression is an important cofactor; and, paradoxically, some level of systemic and localized immune activation in the form of increased Th1 cytokine production (induced either by KSHV infection, HIV infection or unknown causes) is also involved. The Th1 cytokine upregulation initiates an inflammatory-angiogenic process that leads to sites of activated tissue that are vulnerable to KS lesion formation.<sup>52</sup> Recruitment of KSHV-infected cells and other PBMCs to these sites establishes a tissue microenvironment that has high levels of inflammatory cytokines and is increasingly rich in KSHV-infected cells of both macrophagic and endothelial origin. This positively reinforces cell recruitment, and promotes the formation and survival of spindle cells and the production of further cytokines, angiogenic factors and growth factors that contribute to the development of advanced KS lesions.

## CLINICAL MANIFESTATIONS

Most patients with KS present with skin lesions that are typically multiple, pigmented, raised, painless and do not blanch (Fig. 35.2). The earliest cutaneous lesions are often asymptomatic innocuous-looking macular-pigmented lesions, which vary in color from faint pink to vivid purple. Larger plaques occur usually on the trunk as oblong lesions following the line of skin creases. Lesions may develop to form large plaques and nodules that can be associated with painful edema (Fig. 35.3). In addition to a thorough skin examination, inspection of the oral cavity (Fig. 35.4) and conjunctivae (Fig. 35.5) should be undertaken. Oral lesions are a frequent accompaniment that may lead to ulceration, dysphagia, and secondary infection (Fig. 35.4). A nodular form of KS that is frequently associated with lymphedema is seen more commonly in people of African descent and often proves particularly difficult to control.



**Fig. 35.2:** Cutaneous Kaposi sarcoma.



Fig. 35.3: Nodular Kaposi sarcoma.



Fig. 35.4: Oral Kaposi sarcoma.



Fig. 35.5: Ocular Kaposi sarcoma.

**Table 35.2:** The Modified AIDS Clinical Trials Group Staging of KS<sup>5</sup>

	Good risk (all of the following) T0/I0	Poor risk (any of the following) T1/I1
Tumor (T)	Confined to skin, lymph nodes or minimal oral disease	Tumor-associated edema or ulceration Extensive oral KS Gastrointestinal KS KS in other non-nodal viscera
Immune status (I)	CD4 count >150/ $\mu$ L	CD4 <150/ $\mu$ L

The most common sites of visceral KS are the lungs and stomach. Pulmonary KS is a life-threatening complication that usually presents with dyspnea, dry cough and sometimes hemoptysis, with or without fever. Chest X-ray typically reveals a diffuse reticulonodular infiltrate and pleural effusion. Gastrointestinal lesions are usually asymptomatic but may bleed or cause obstruction. The diagnosis is usually confirmed at endoscopy. The prognosis of patients with AIDS-KS depends upon both the stage of the KS, the level of immunosuppression, and the response to anti-HIV therapy. KS is staged using the AIDS clinical trials group modified staging classification (see Table 35.2).<sup>53</sup>

## TREATMENT

For AIDS-KS patients with symptomatic disease or life threatening visceral disease prompt effective therapy is usually merited, while for patients with asymptomatic indolent lesions HAART alone may result in complete regression. Criteria for evaluating response to therapy have been established (see Table 35.3).<sup>54</sup>

## Highly Active Antiretroviral Therapy

There has been a fall in the incidence of KS both as a first AIDS diagnosis and a subsequent manifestation in HIV seropositive cohorts from established market economies. This decline in KS coincides with the introduction of highly active antiretroviral therapies (HAART) and the relative risk of developing KS is significantly lower among people receiving HAART regimens.<sup>55–59</sup> Indeed the majority of patients with newly diagnosed KS are HAART naïve or have virological evidence of failure with detectable HIV viral loads. A number of case reports and small studies documenting responses of KS to HAART have been published. A study of 78 patients with established KS has demonstrated that the introduction of HAART therapy is associated with a prolongation of the time to treatment failure of KS.<sup>60</sup> Thus HAART therapy has a major influence both on the epidemiology and clinical progression of KS without apparently having a direct effect upon the causative herpesvirus, HHV-8. The postulated mechanism of this effect is the immune reconstitution of cytotoxic T-lymphocyte responses to HHV-8. The response rate to HAART alone is around 60–70% but lesions may take 6–12 months to fade.



**Table 35.3:** Response Criteria for HIV-Associated Kaposi Sarcoma

<b>Complete response (CR)</b>
The complete resolution of all KS with no new lesions, lasting for at least 4 weeks. A biopsy is required to confirm the absence of residual KS in flat lesions containing pigmentation. Endoscopies must be repeated to confirm the complete resolution of previously detected visceral disease.
<b>Clinical complete response (CCR)</b>
Patients who have no detectable residual KS lesions for at least 4 weeks but whose response was not confirmed by biopsy and/or repeat endoscopy.
<b>Partial response (PR)</b>
One or more of the following in the absence of (i) new cutaneous lesions, (ii) new visceral/oral lesions, (iii) increasing KS-associated edema, (iv) a 25% or more increase in the product of the bidimensional diameters of any index lesion: 1. A 50% or greater decrease in the number of measurable lesions on the skin and/or in the mouth or viscera. 2. A 50% or greater decrease in the size of the lesions as defined by one of the following three criteria (a) a 50% or more decrease in the sums of the products of the largest bidimensional diameters of the index lesions; (b) a complete flattening of at least 50% of the lesions; (c) where 75% or more of the nodular lesions become indurated plaques.
<b>Stable disease (SD)</b>
Any response that does not meet the above criteria.
<b>Progressive disease (PD)</b>
Any of the following: 1. A 25% or more increase in the product of the bidimensional diameters of any index lesion. 2. The appearance of new lesions. 3. Where 25% or more of previously flat lesions become raised. 4. The appearance of new or increased KS-associated edema.

## Intralesional Chemotherapy

Localized therapies are advocated for patients with limited cutaneous disease. Intralesional injection of a dilute solution of vinblastine (0.2 mg/mL) using volumes of up to 0.5 ml per lesion is an effective, easy, and well-tolerated treatment for lesions under 1 cm in diameter. Intralesional vinblastine has no significant systemic effects and injections may be repeated 2 or 3 times. This approach is also valuable for small intraoral and gingival lesions.

## Radiotherapy

Larger cutaneous lesions may be treated with radiotherapy and local control is generally achieved. For cutaneous lesions either a single fraction of 8Gy or 16Gy in four fractions is routinely used. Although the response rate and duration of local control may be better with fractionated regimens compared with single fraction treatment, toxicity and patient convenience are worse. Cosmetic improvement is usually achieved although there may be a halo appearance on account of the depigmented margin around treated lesions. Severe mucositis and acute edema reactions may

follow radiation treatment of the oral cavity and feet and for this reason treatment is given in four fractions at weekly intervals. Recurrence of the tumor is common and therefore radiotherapy treatment is usually reserved for symptomatic and cosmetically disturbing lesions.

## Chemotherapy for KS

Chemotherapy is advocated for advanced cutaneous and visceral KS but is not merited for early disease in view of the potential response to HAART. Early single agent studies confirmed the activity of a number of cytotoxic agents. In particular, anthracyclines, vinca alkaloids, bleomycin, and etoposide were found to have clinical activity with observed response rates of 20–60%. In Europe, bleomycin and vincristine (BV) was the most frequently prescribed chemotherapy for KS until the mid-1990s. It is considered safe and effective, the main toxicity being peripheral neuropathy although reduced lung transfer factor is seen with high cumulative bleomycin doses. The addition of adriamycin (ABV) was widely practiced in America and may increase the response rate marginally but results in myelosuppression and alopecia.

## Liposomal Anthracyclines

Liposome encapsulation of anthracyclines constituted a considerable advance in the chemotherapy of KS. The advantages of liposomal formulation include increased tumor uptake and hence favorable pharmacokinetics. Moreover, the liposomal forms are less cardiotoxic than the parent anthracyclines. Both liposome encapsulated daunorubicin (Daunoxome 40 mg/m<sup>2</sup> every 2 weeks) and the pegylated liposomal doxorubicin (Caelyx 20 mg/m<sup>2</sup> every 3 weeks) have been shown to have good antitumor activity. The toxicity profile is better than for other anthracyclines, with no reported cardiotoxicity even with high cumulative dosages and rarely significant alopecia, however there remains considerable myelosuppression, and occasional emesis. In addition, infusion related hypotension and hand/foot syndrome are novel side effects seen with these liposomal formulations. In randomized comparisons of liposomal doxorubicin compared to both ABV and BV as first line therapy for KS, response rates were higher in the Caelyx arms.<sup>61,62</sup> Liposomal anthracyclines are considered first line chemotherapy for advanced KS.

## Paclitaxel

Paclitaxel has been shown to have single agent activity against KS and has a valuable role in the management of refractory disease. The toxicities of paclitaxel are well-recognized although appear to be no worse in patients with HIV than in other groups treated with equivalent dosages. Two studies of refractory KS have shown response rates of 53% and 71% and median response durations of 7.4 and 10.4-month.<sup>63,64</sup> These results have led to the rapid acceptance of paclitaxel (100 mg/m<sup>2</sup> over 3 hours every 2 weeks) as the treatment of choice for anthracycline refractory KS.

## Multicentric Castleman Disease

### PATHOGENESIS

Multicentric Castleman disease (MCD) is a rare, atypical lymphoproliferative disorder of the plasma cell type. It is characterized clinically by generalized lymphadenopathy and evidence of multiorgan involvement.<sup>65</sup> Its close association with KS, particularly in AIDS patients, prompted Soulier et al. to search for the presence of KSHV sequences in MCD samples.<sup>66</sup> They, and others,<sup>67</sup> found that KSHV DNA is detected in MCD lesions from all HIV-related and about 40% of HIV-unrelated cases of MCD. It is therefore likely that there is more than one cause for this unusual disease. Nonetheless, a correlation between increased KSHV viral load in peripheral blood mononuclear cells and clinical MCD exacerbations supports a role for KSHV in MCD pathogenesis.<sup>68</sup> Recently, KSHV-positive MCD has been recognized as a distinct subset of MCD and designated plasmablastic MCD, since it features the presence of large plasmablastic cells all of which harbor KSHV.<sup>69</sup> Unlike KS and PEL, the tumor cells from MCD, express both latent and lytic KSHV proteins.<sup>21,22</sup>

### DIAGNOSIS

The diagnosis of MCD is established histologically by lymph node biopsy or if necessary after splenectomy. The characteristic features are interfollicular plasmablasts that express the KSHV latent nuclear antigen (LANA). These plasmablasts also express high levels of  $\lambda$  light-chain restricted IgM, but are polyclonal and do not contain somatic mutations in their IgG genes, suggesting that they arise from naïve B-lymphocytes.<sup>70</sup> Occasionally, these plasmablasts join together to form clusters or “microlymphomas” and may progress to monoclonal plasmablastic lymphomas.<sup>69</sup>

### CLINICAL MANIFESTATIONS

On examination, patients have diffuse lymphadenopathy, hepatosplenomegaly, and may have ascites, edema, and effusions both pulmonary and pericardial. The clinical manifestations include an acute interstitial pneumonitis<sup>71,72</sup> and hemophagocytic syndrome<sup>73</sup> and less frequently neuropathic problems including polyneuropathies, leptomeningeal, and CNS infiltration as well as myasthenia gravis.<sup>74</sup> Laboratory investigations may reveal thrombocytopenia, anemia, hypoalbuminemia, and hypergammaglobulinemia. The systemic manifestations are thought to be due to interleukin-6 secretion either directly by the tumor or in response to the disease. MCD is a relapsing and remitting disease and the definition of an “attack” has been proposed as a combination of fever and a raised serum C-reactive protein in the absence of other etiology plus three of the following symptoms: peripheral lymphadenopathy, splenomegaly, edema, pleural effusion, ascites, cough, nasal obstruction, xerostomia, rash, central neurological symptoms, jaundice or autoimmune hemolytic anemia.<sup>75</sup>

### TREATMENT

The optimum treatment for Castleman disease remains uncertain. The prognosis is poor with a median survival of 14 months in one published series.<sup>76</sup> However, earlier recognition of the diagnosis and treatment with single agent chemotherapy, monoclonal antibodies to CD20, and splenectomy has recently been shown to result in high remission rates and prolonged survival.<sup>75,77,78</sup> The natural history of Castleman disease follows a relapsing and remitting course and there is a high risk of systemic NHL.<sup>79</sup> High plasma cell-free levels of HHV8 DNA viral load appear to reflect disease activity in Castleman disease and may be useful in diagnosing and monitoring the disease.

## Primary Effusion Lymphoma

Primary effusion lymphoma (PEL) is a high grade non-Hodgkin B-cell lymphoma that usually occurs in the context of HIV-infection. PEL presents with lymphomatous effusions in body cavities such as the pleural, pericardial, and peritoneal spaces in the absence of a solid tumor mass. PEL express an indeterminate immunophenotype with clonal immunoglobulin gene rearrangements. PEL was first defined as a unique disease (originally under the name body cavity-based lymphoma) when Cesarman et al. demonstrated the presence of high levels of KSHV DNA in all cases of this atypical lymphoma, but not in any other HIV- or non-HIV-related non-Hodgkin lymphoma.<sup>80</sup> By definition, therefore, PEL patients must show evidence of KSHV infection although the mechanisms by which KSHV promotes oncogenesis in PEL are not fully understood. In addition many PEL are coinfecting with EBV. The clinical management of PEL does not differ from the HIV associated NHL. Patients present with a median CD4 count of  $90/\mu\text{L}^3$  while the median survival in one study is just 5 months.

### Summary

KSHV, which is also known as HHV8 is a gammaherpesvirus identified in 1994 that is implicated in the pathogenesis of not only all forms of Kaposi sarcoma but also some cases of primary effusion lymphomas and multicentric Castleman disease.

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# section **vii**

## **BACTERIAL SEXUALLY TRANSMITTED INFECTIONS** — *Jonathan Ross*

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## Introduction

Syphilis is a chronic sexually transmitted disease caused by infection with a spirochaete bacterium *Treponema pallidum subsp. pallidum*. It is systemic from the outset, capable of involving every structure of the body in its course, and distinguished by florid manifestations on one hand and years of completely asymptomatic latency on the other. It can simulate many diseases and present to a wide range of medical specialities.<sup>1</sup>

The disease is broadly divided into infectious or early syphilis and non-infectious or late syphilis. Infectious syphilis is a disease of considerable public health importance. This importance particularly relates to adverse pregnancy outcomes (stillbirth and congenital syphilis) and the facilitation of HIV transmission by the ulcerative and inflammatory lesions of primary and secondary syphilis.<sup>2</sup> Syphilis is most infectious through sexual contact or from mother to foetus during the primary and secondary stages; however, transmission may also occur during the period of early latency.

## Epidemiology

Syphilis remains a common infection worldwide and the World Health Organization (WHO) estimated that in 1999 12 million individuals developed early syphilis<sup>3</sup> and it was estimated that in 2006 between 750,000 and 1.5 million pregnancies were affected by syphilis.<sup>4</sup> Most infections are in sub-Saharan Africa and south Asia (in community prevalence studies of women in India the prevalence of infection varies from 0.2% to 10.5%).<sup>5</sup> There is some evidence that the community prevalence of syphilis is falling in some populations in India with the RPR reactivity in voluntary donors decreasing from 0.4% in 2004 to 0.09% in 2006–07.<sup>6</sup> In a sexually transmitted infection (STI) clinic in Gambia, West Africa, the prevalence of serological syphilis dropped from 11.2% in 1994 to 1.5% in 2007.<sup>7</sup> In the US and Europe, transmission of syphilis became rare in the 1970s and early 1980s but has since re-emerged as an important infection.<sup>8</sup> In the US in the 1980s there was a sustained epidemic of early syphilis associated with crack cocaine use and disproportionately affecting African-Americans.<sup>9</sup> After the break-up of the Soviet Union, the social

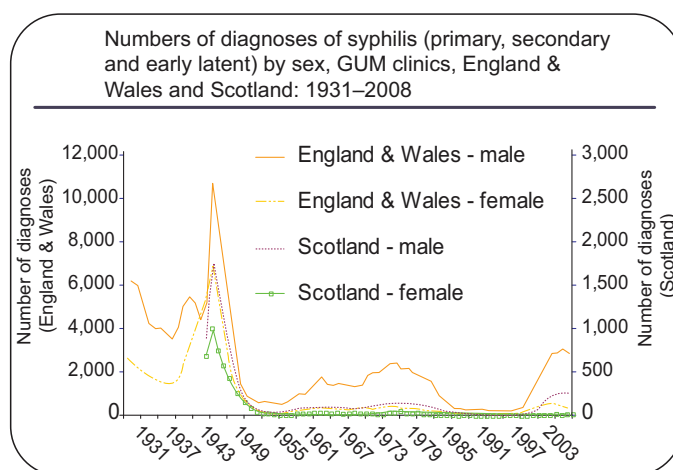


Fig. 36.1: Natural history of syphilis (Modified and redrawn from Reference 211).

disruption and collapse of public health services resulted in a huge epidemic of syphilis that affected the syphilis rates in neighboring countries.<sup>10</sup> In Western Europe since the late 1990s, there has been a re-emergence of syphilis, particularly affecting gay men many of whom have previously been diagnosed with HIV.<sup>11</sup> The numbers of men and women diagnosed in STI clinics in the UK since 1931 are shown in Fig. 36.1. This graph shows the epidemic of syphilis during the Second World War and its re-emergence among gay men in the 1970s and 1980s. This is followed by its virtual eradication as an endemically transmitted infection in the mid 1980s and re-emergence in gay men in the late 1990s.

## Incubation Period

After sexual contact with someone who has early syphilis, approximately one-third of individuals will develop a primary chancre. The incubation period (IP) for primary chancre has been found to vary in natural and experimental infections, and probably depends on inoculum size. The mean primary IP (period between infection and appearance of primary chancre) in experimental infection has been found to be 25 days and in

the natural infection 31 days. Although the commonly quoted range of IP is 9–90 days, the variation is usually much less. The available data indicate that in most cases, the primary IP varies between 3 and 4 weeks.<sup>12</sup>

### Primary Chancre, Secondary IP, and Secondary Eruption

After the primary IP a primary chancre appears at the site of inoculation. Most primary chancres heal before secondary lesions emerge. Virtually all people with syphilis develop secondary syphilis, but the manifestations may be so mild that they may go unnoticed or do not prompt individuals to seek treatment.<sup>13</sup> The average duration for a chancre to heal is 12 days. However, in 12–34% women and 56–63% men, the chancre may persist and be present during the appearance of the secondary rash.

The average secondary IP (period between contact and appearance of secondary rash) is approximately 8 weeks. In some people, the eruption may develop later, but almost always within 6 months. The data from the Oslo study suggest that the symptoms of secondary disease last for an average of 3.6 months with a range of 1–12 months.<sup>14</sup>

Approximately 25% of individuals develop a relapse of secondary disease. Further, 5% of patients may have 2 relapses and 1%, 3 relapses. Two-thirds of these relapses occur within 6 months, 90% within one year, 95% within 2 years, and 100% within 5 years.<sup>15</sup>

### Latent Stage

After the secondary stage resolves, the individual then remains in an asymptomatic stage, termed “latency.” During this stage, the only evidence of infection is positive syphilis serology. An arbitrary distinction between early and late latent syphilis is used primarily to guide decisions regarding treatment. As most relapses of the secondary syphilis rash occur in the first year of infection, this period is defined as early latent (infectious) syphilis and the later period as late latent (non-infectious) syphilis by the European (European Centre for Disease Prevention and Control)<sup>16</sup> and Centers for Disease Control and Prevention (CDC) (US) guidelines.<sup>17,18</sup> WHO<sup>19</sup> and the UK<sup>20</sup> use a two-year period to define these terms.

### Late Syphilis

Approximately, two-thirds of patients with late latent syphilis are considered to have spontaneous cure with no clinical or pathological evidence of infection.

About 15–40% patients develop recognizable late complications of syphilis. The results of Oslo study showed that over a period of 35 years, late benign (gummatous) syphilis had developed in 15.8% of patients. Cardiovascular complications developed in 10.4% (14% of male and 8% of female) patients and neurosyphilis in 6.6% (9% of male and 5% of female) of patients. In the Oslo study, syphilis was considered as a cause of death in about 10% of patients. Late syphilis is rarely encountered in immunocompetent

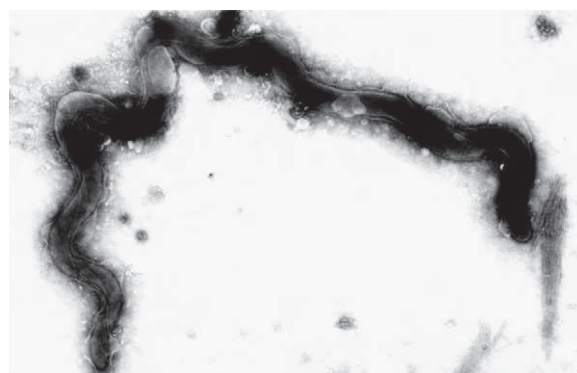
persons these days which is probably partly due to better syphilis control and effective treatment and partly because of the benefit of the inadvertent use of antibiotics for other diseases.<sup>13</sup>

### Biology of *Treponema Pallidum*

Until recently the taxonomy of spirochetes was not well-developed because of difficulties experienced in growing many important species of spirochaetes *in vitro*. The information about their biochemical and other phenotypic properties was lacking, and classifications, often inappropriate, were largely based on morphological, ecological, and epidemiological criteria. *T. pallidum* (Fig. 36.2) is the causative agent of syphilis, however, because of close genetic homology, *T. pallidum* of venereal syphilis (*subsp. pallidum*), yaws (*subsp. pertenue*), and endemic syphilis (*subsp. endemicum*); all have been assigned to the same species.<sup>21,22</sup> Recently, however, a genetic signature was defined in the 15-kDa lipoprotein gene (*ttp15*) of *T. pallidum subsp. pallidum* that distinguishes it from *T. pallidum subsp. pertenue* and *T. pallidum subsp. Endemicum*.<sup>23</sup> *T. carateum*, the causative agent for pinta, is still considered a separate species due to the lack of genetic information.<sup>24</sup>

Nichols first isolated *T. pallidum* in 1912 from the spinal fluid of a patient with syphilis with neurological involvement. Since then, this strain has been maintained in the laboratory in rabbit testicles for experimental purposes and known after him as Nichols strain.<sup>25</sup> Subsequently, in 1982, Penn et al.<sup>26</sup> isolated another strain from human chancres and cultivated it in rabbit testicles. This strain was less virulent than Nichols strain.

*T. pallidum* is a thin, delicate, pale, motile, regularly close-coiled spiral spirochete with tapering ends. Because of its thinness, it cannot be visualized by conventional light microscopy, and dark ground illumination (DGI) is required to observe it. Under DGI, it can be recognized by its characteristic movements, which include slow forward and backward movement, rotating on its long axis like a corkscrew, and a compression, expansion and bending (flexuous) movement.<sup>27</sup> *T. pallidum* varies from 8 to 16  $\mu\text{m}$  in length and 0.1–15  $\mu\text{m}$  in width.<sup>28</sup> The wavelength of the



**Fig. 36.2:** Negative stain electron micrograph of *Treponema pallidum*. Courtesy: Arya OP, Hart CA, eds. *Sexually Transmitted Infections and AIDS in the Tropics*. Wallingford: CAB International, 1998; Fig. 7.1.2.



organism is about 0.9  $\mu\text{m}$  with amplitude of 0.2  $\mu\text{m}$ . It has 8–20 regularly placed, rigid coils with a distance of 1  $\mu\text{m}$  between each coil. The terminal part of *T. pallidum* is formed by an acron-like nose piece of about 50 nm  $\times$  60 nm. These nose pieces are thought to be responsible for attachment of the organism. The central cytoplasmic body is enveloped in a 7 nm thick triple layered cytoplasmic membrane or outer membrane. This contains 100-fold less membrane spanning proteins compared with outer membranes of other typical gram-negative bacteria.<sup>29,30</sup> The low-protein content of exposed outer membrane helps the organism evade the host immune response during chronic infection.<sup>31</sup>

Three or four endoflagella are inserted in a row on the tapering terminal portion at each end of the organism. They originate from the subterminal regions of cytoplasmic body. Endoflagella from both ends of the cell extend up to more than half of the length of the organism and interdigitate over its central portion.<sup>32–33</sup> These endoflagella are probably responsible for the characteristic motility of treponemes.

The genome sequence of *Treponema pallidum subsp. pallidum* has recently been elucidated.<sup>34</sup> The sequence and predicted function of over 1000 genes will greatly facilitate research in the genetic characteristics, physiology, antigenic structure and pathogenesis of this bacterium. The organism has been shown to have extremely limited metabolic capabilities for instance it is unable to synthesize ATP, lacks proteins for iron transfer and is unable to manufacturing some nucleotides and most amino acids. On the other hand many of the genes whose function has been elucidated code for transport proteins confirming that *T. pallidum* is highly dependent on its host and explaining the fastidious nature of this organism *in vitro*.<sup>35</sup> These advances are expected to promote the refinement of conditions for *in vitro* culture, an improvement of diagnostic tests, the development of vaccines and an improved understanding of pathogenesis and manifestations of syphilis.<sup>33</sup>

## CULTURE

*T. pallidum* is considered a non-cultivable bacterium *in vitro*. However, the organism has been successfully grown in mammalian tissue culture cells.<sup>34</sup> However poor yields are obtained and serial subcultures *in vitro* are difficult to achieve. Therefore, the only practical method for the culture of *T. pallidum* at present is inoculation in rabbit testes. Treponemal suspension is injected into the body of the testis. After a week, the testis becomes firm and then, in the next few days, enlarges rapidly due to a diffuse orchitis.<sup>36</sup>

Although, the organism was considered a strict anaerobe in earlier reports, it has now been realized that an oxygen concentration of about 3% in the gaseous phase is helpful for optimum growth.<sup>37,38</sup> The balance of oxygen utilization and toxicity is the key to the survival and growth of *T. pallidum*.

The metabolic capabilities and adaptability of *T. pallidum* are minimal. This relative deficiency can be explained by the absence of many metabolic pathways, including tricarboxylic acid cycle, components of oxidative phosphorylation and most biosynthetic pathways. The genome sequencing of *T. pallidum* has confirmed

the inability of the organism to synthesize enzyme cofactors, fatty acids, and nucleotides *de novo*.<sup>35,39,40</sup>

*T. pallidum* is an extremely delicate organism that is sensitive to low concentrations of detergents, desiccation and raised temperature. Exposure of *T. pallidum* to 41.5°C for 1 hour is lethal and before the discovery of penicillin, induced fever, either by malaria therapy or artificially by “Kettering hyper-therm,” was a popular and partially effective treatment modality for syphilis.<sup>41</sup>

## Immunology of Syphilis

Animal experiments during the earlier half of the 20th century have shown that shortly after the development of a primary lesion, a second primary lesion cannot be easily produced on re-inoculation. This phenomenon is known as chancre immunity.<sup>42</sup> Re-inoculation of a rabbit on the site of a previous chancre met with decreasing success as the age of first infection increases. However, human inoculation experiments carried out during the same period showed that a chancre can be produced in man while the first chancre is progressing, while inoculation of organisms during the secondary stage produces papules and during tertiary stage, gummata. Immunity to chancre formation is well-marked in early latency, and this lessens with the passage of time.<sup>42</sup>

*Treponema pallidum subsp. pallidum* establishes a lifelong chronic infection in the absence of appropriate treatment. The immune response evasion mechanisms employed by *T. pallidum* are poorly understood.<sup>43</sup> One of the factors contributing to immune evasion is poorly exposed immunogenic surface proteins in the outer membrane (*T. pallidum* rare outer membrane proteins-TROMPs).<sup>44</sup> These highly immunogenic proteins of *T. pallidum* are lipoproteins anchored predominantly to the periplasmic leaflet of the cytoplasmic membrane, protected by the less immunogenic outer membrane.<sup>45</sup> In addition, *T. pallidum* may have a complex system of antigenic variation for immune evasion.<sup>46</sup>

The cell-mediated inflammatory processes triggered by treponemes within infected tissues have two distinct, yet interrelated, consequences. On one hand, they cause the tissue damage which is responsible for clinical manifestations, while on the other hand, they are responsible for the clearing of treponemes, a prerequisite for the resolution of lesions.<sup>47,48</sup> Cellular infiltrates in syphilitic lesions are mainly composed of lymphocytes, macrophages and plasma cells. Immunohistochemical analyses have shown that these infiltrating cells are activated T cells and that these T cells release cytokines consistent with a Th1 type of response.<sup>49,50</sup> Dendritic cells have a key role in presenting *T. pallidum* to T lymphocytes in the regional lymph nodes causing T lymphocytes to proliferate and migrate to the site of infection. In the lesions of primary syphilis helper (CD4+) T cells predominate and in secondary syphilis lesions cytolytic (CD8+) cells predominate. These T cells activate macrophages and stimulate B cells to produce antibodies against *T. pallidum* and it is likely that the resulting inflammatory response causes the clinical manifestations of syphilis and tissue damage.<sup>51</sup> In one study, a delayed tuberculin type skin responses were induced in

patients with late acquired or congenital syphilis by the repeated inoculation of material obtained from rabbit syphilitic testes. However, this test is usually negative in patients with early syphilis.<sup>42</sup>

This partial “anergy” in the early infectious stage disappears with treatment or with the progression to non-infectious late stage disease. It is specific to syphilitic antigens, and reaction to other intradermal tests remain normal in these patients. This partial inhibition of the cell mediated immune response is thought to be responsible for the persistence of infectiousness for prolonged periods and for the ease of demonstrating treponemes in tissues. In late stages, treatment has no effect on the positive intradermal test with syphilitic antigens. The initial inhibition of the immune response in early syphilis is reflected by the finding of depletion of lymphocytes in the para-cortical (thymus dependant) areas of lymph node; however, the mechanism of this active suppression of cell mediated immunity is not understood. A plasma factor depresses phytohemagglutinin lymphocyte stimulation in infectious syphilis. Antigen-antibody immune complexes formed during early stages of syphilis have also been thought to suppress delayed hypersensitivity reactions. The role of genetic factors is not clear.<sup>52</sup>

Several experimental studies have provided evidence in support of a major role of humoral immunity in defence against *T. pallidum*.<sup>53,54</sup> These include immune serum passive protection.<sup>55,56</sup> inhibition of *T. pallidum* adherence and invasion of cultured cell monolayers by immune serum, immune serum mediated phagocytosis of *T. pallidum* by rabbit peritoneal macrophages,<sup>57</sup> and immune serum complement-dependent treponemicidal antibody.<sup>58</sup> Further, it has been demonstrated that a close quantitative correlation exists between the development of acquired resistance and the level of treponemicidal antibody, suggesting that killing antibody plays a major role in the acquisition of protective immunity.<sup>59</sup>

## Pathogenesis

*T. pallidum* is presumed to penetrate through small breaks in the skin or mucosa.<sup>60</sup> Intact skin, and to a lesser extent, intact mucous membranes, do provide a barrier to syphilitic infection in man. However, animal experiments have shown that male rabbits may be infected by exposing the normal mucous membrane of the prepuce to a treponemal suspension suggesting that protection provided by intact mucous membrane is not absolute.<sup>61</sup> Magnuson et al.<sup>62</sup> in their study on four human volunteers, successfully produced dark field positive lesions by injecting virulent *T. pallidum* in doses of 10, 100, 1000 and 10,000 organisms on the forearm.

The 50% infectious dose was calculated to be 57 organisms.<sup>61</sup> Animal studies have shown that the organisms appear within minutes in lymph nodes and disseminate widely via the bloodstream within hours.<sup>63,64</sup> How it enters the cell is not exactly known. It has been shown to adhere rapidly to mammalian cells in tissue culture.<sup>65</sup> It requires an epithelial

surface to attach and penetrate the tissue.<sup>66</sup> Attachment may occur by specific attachment ligands.<sup>67–69</sup> *T. pallidum* increases interstitial collagenase levels when added to human dermal fibroblast culture. This suggests that *T. pallidum* can stimulate host human fibroblasts to increase the synthesis of interstitial collagenase which may act as a virulence factor and probably help the organism to penetrate the cell.<sup>70</sup>

After penetration, the organisms multiply slowly at the site of inoculation without producing a clinically overt lesion. When the number reaches a threshold level, unknown mechanisms induce formation of the primary lesion, which is a raised, firm, erythematous, and painless ulcer (which may be preceded by a papule which then ulcerates). The primary lesion is full of organisms which are usually easily detected by dark ground examination. A combined humoral and cell-mediated immune response appears to eliminate the pathogen locally resulting in complete healing. Spirochaetemia occurs early during the evolution of the primary chancre, therefore healing of primary lesion does not prevent development of the secondary stage. Most patients progress to the secondary stage, characterized by lesions scattered on the skin and (usually asymptotically) many other organs. Like the primary lesion, organisms are found in large numbers in the secondary lesions.<sup>22</sup> At this stage, circulating immune complexes have been identified, which may contain a small number of treponemal antigens.<sup>71</sup> In the secondary stage there are a number of autoimmune responses that have been reported<sup>22</sup> including to cardiolipin, fibronectin, collagen, laminin, and creatine kinase. The antibody response against treponemes is responsible for the relatively mild nature of generalized disease, which might otherwise resemble generalized, multiple primary chancres.

The secondary stage also involutes spontaneously and is followed by a period of long latency, which may last many years or result in spontaneous cure of infection. It is assumed that during latency treponemes are sequestered in small numbers at immunologically protected sites in the body. Eventually the tertiary stage may develop, which may manifest either in its serious form as cardiovascular syphilis or neurosyphilis, or as more benign gummatous lesions in skin and other organs.

During this stage, treponemes are characteristically sparse with the exception of general paresis, in which there is often an abundance of treponemes in cerebral tissue.<sup>52</sup> Some immunological mechanisms rather than direct damage by treponemes are thought to play important role in the pathogenesis of late syphilis. The local cellular response in the affected tissues in tertiary syphilis resembles a delayed type of hypersensitivity reaction to a very small number of organisms.

## Transmission of Disease

Syphilis spreads through contact with infectious lesions or body fluids. It is acquired through direct sexual contact with an infected person in the early stages of disease or from mother to foetus. Late stages of syphilis are non-infectious.

Studies from the pre-antibiotic era found that nearly 30% of sex partners of persons with primary and secondary syphilis develop the disease.<sup>72</sup> Later studies have shown that almost half of the homosexual or heterosexual contacts of patients with primary and secondary syphilis were infected.<sup>73</sup> Epidemiologic analysis from sub-Saharan Africa showed a transmission possibility in early infectious syphilis of approximately 0.3 from male to female and 0.2 from female to male. The variable factors that influence transmission of infection include the number of exposures, the type of sexual activity, and the morphology and distribution of lesions in the infected partner or partners.<sup>74</sup>

Rarely, non-sexual, non-materno-fetal transmission of the disease can occur in healthcare workers, and in infants and children. The term “syphilis brephotrophica” was coined by Jadassohn referring to syphilis transmitted while performing baby care or handling children.<sup>75</sup> The term lues insontium has also been used to describe non-sexual transmission in general.<sup>76</sup> Studies in the pre-antibiotic era suggested a rate of about 23% of non-sexual transmission of syphilis in children.<sup>76,77</sup> However at that time, the magnitude of sexual abuse was largely unrecognized. Current studies have shown that in the US, as many as 1 in 4 girls and 1 in 7 boys are victims of child sexual abuse and majority of these victims do not show any physical signs. Therefore, the incidence of non-sexually acquired syphilis in children is likely to be much less than that reported in the pre-antibiotic era.<sup>78</sup> Breastfeeding does not result in the transmission of syphilis, unless an infectious lesion is present on the breast. In patients with syphilitic lesions on the lips or oral cavity, kisses may also be a mode of transmission.<sup>79</sup>

A rare route of transmission of syphilis is parenteral transmission via injection drug use or by blood components. Routinely, donated blood is screened for syphilis by serological tests. However, these tests may be negative in some patients with early primary syphilis, who may have a spirochaetemia. However, treponemes remain alive in blood stored at 4°C for only for 2–3 days, minimizing the risk of transmission.<sup>80</sup> In addition to this many patients who receive blood products also receive antimicrobials for their disease, which are treponemocidal. Thus the chances of transfusion transmitted syphilis are minimal. Patients receiving fresh blood are at relatively higher risk of transmission if the donor is in the window period for the serological diagnosis of primary syphilis. Transfusion transmitted syphilis presents directly as secondary syphilis (bypasses primary stage) and is known as “syphilis d’emblée.”<sup>81</sup> Recently, transmission of syphilis during hemodialysis has been reported in patients with end-stage renal disease.<sup>82</sup> Most of the patients who acquired syphilis by hemodialysis were found to have latent disease.<sup>83</sup>

## Clinical Features

### PRIMARY SYPHILIS

After an IP of 9–90 days, the primary chancre appears at the site of inoculation. A small dull red macule appears initially, which soon becomes a papule and subsequently ulcerates to form a



**Fig. 36.3:** Classic hunterian chancre—a single, painless, indurated ulcer with clearly defined borders.

chancre, which is the classical lesion of primary syphilis. The classic hunterian chancre is a single, painless, indurated ulcer, round to oval in shape, clearly defined, with rolled borders and a “ham colored” smooth base but sometimes may be covered with a grayish slough or slightly hemorrhagic crust (Fig. 36.3). The size of the chancre varies from 0.3 cm to 3 cm.

The induration of ulcer on the inner side of prepuce often gives rise to flip on retraction of the preputial skin. This sign is known as the “dory flop.” Kissing ulcers occur on the urethral meatus and coronal sulcus (Figs. 36.4 and 36.5). An ulcer may occur at the hilt of the shaft of the penis, when it is called a “condom chancre.”<sup>84</sup> Though the classical clinical features are quite typical for chancre, these may be absent in almost half of the patients. In one prospective series of patients with primary syphilis one third of HIV negative patients and two thirds of HIV positive patients presented with multiple primary ulcers.<sup>84</sup> So, multiple chancres are not uncommon and in various patient series, have been reported



**Fig. 36.4:** An indurated papule of primary chancre with inguinal lymphadenopathy. The intense inflammation seen in the lymphnode is due to secondary bacterial infection. *Courtesy: Dr. Somesh Gupta.*

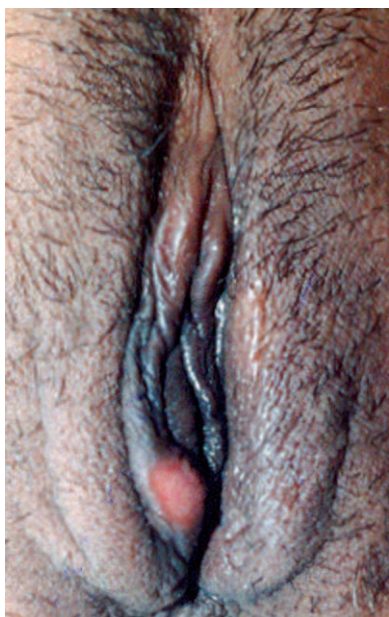




**Fig. 36.5:** Primary syphilis—kissing ulcer in coronal sulcus.

to occur in 18–53% of patients with primary syphilis.<sup>85,86</sup> The classic features of primary chancre (painless, indurated, single ulcer with a relatively clean base) have a sensitivity of only 31% but a specificity of 98%.<sup>87</sup> Anderson noted that painful lesions were present in 25% of the patients with primary syphilis and non-indurated lesions were seen in 33%.<sup>88</sup> Mixed infection with *Haemophilus ducreyi* and herpes simplex are common and may produce atypical lesions. Administration of antimicrobials can also change the clinical picture at presentation.

In men, the chancre on the genitalia is seen on the coronal sulcus (35%), glans (29%), shaft (22%), prepuce (19%), frenulum (10%), and in the urinary meatus (1%). In women, genital chancres are seen on the vulva, vagina, or the cervix (Figs. 36.6 and 36.7). The cervix is involved in as many as 44% of patients; however, this is rarely detected unless speculum examination is carried out.<sup>89</sup>



**Fig. 36.6:** Primary chancre on the vulva.



**Fig. 36.7:** Primary chancre in the cervix. Courtesy: Arya OP, Hart CA, eds. *Sexually Transmitted Infections and AIDS in the Tropics*. Wallingford: CAB International, 1998;Plate 32.

Extragenital chancres occur in 12–14% of patients with primary syphilis.<sup>90</sup> These usually result from contact with genital or extragenital lesions in the partner during sexual foreplay, or during anal or oral sex. Rarely, they may occur as a result of inoculation with infected syringes and tattoo needles or a human bite.<sup>91–93</sup> Anorectal chancre is more frequently seen in homosexual men who have receptive anorectal sex. Chancres at these locations are often asymptomatic and may mimic anorectal cancer.<sup>94</sup> In a large series, anorectal chancres were seen in 34% of homosexual men and 7% of women. Oral lesions were seen in 1–3% of women and homosexual men but are likely to be considerably commoner than this and are likely to be either sub-clinical or undiagnosed. A recent study from the UK suggested that up to 35% of syphilis infections among gay men were attributable to oral sex suggesting that oral chancres are likely to be common. Chancres at these locations are exceedingly rare in heterosexual men.<sup>95</sup> Syphilitic chancre may also appear on hands and arms, and rarely, it may present as paronychia.<sup>96</sup>

Chancres are accompanied by regional lymphadenopathy in 50% of cases, which resolves spontaneously in about 4–6 weeks.

*Monorecidive or chancre redux* is the recurrence of a primary sore at the site of the original lesion.<sup>97</sup> It is considered as by some clinicians to be a form of relapse.<sup>1</sup>

*Pseudochancre redux* also occurs at the site of the original chancre; however, unlike true chancre redux, it is noninfectious granulomatous lesion of late syphilis from which treponemes cannot be recovered. The histopathology of this lesion shows granulomatous foci with necrosis and giant cell reaction.

The syphilitic balanitis of Follman is an inflammatory reaction of glans penis in primary syphilis to *T. pallidum*, which may develop instead of, before, after or simultaneously with the primary chancre. Numerous treponemes are present in the lesion which can be demonstrated by DGI or in histologic sections. The balanitis is superficial as the organisms are seen only in epidermal cell layers. The condition is likely to be much more common than is generally supposed, as many cases go unnoticed or unreported.<sup>98</sup>



Syphilis d'emblée is defined as syphilis without chancre. It is a consequence of direct inoculation into the blood as a result of transfusion of infected blood or blood components or puncture with an infected needle. As the inoculation is directly into the blood, generalized syphilis develops without a local reaction.

**Complications** of primary chancre include edema, phimosis, erosive balanitis, lymphangitis, and thrombophlebitis of the dorsal vein. Phagedenic chancre is due to co-infection with fusospirochaetes. It is characterized by necrotizing perforation of prepuce, or in some patients, gangrene.<sup>99</sup>

**Differential diagnosis:** Other STI-related causes of genital ulcers like genital herpes, chancroid, donovanosis, and lymphogranuloma venereum (LGV) should be ruled out. Non-STI related causes like Behçet disease, Crohn disease, squamous cell carcinoma, and fixed drug eruption should also be considered in the differential diagnosis.

## SECONDARY SYPHILIS

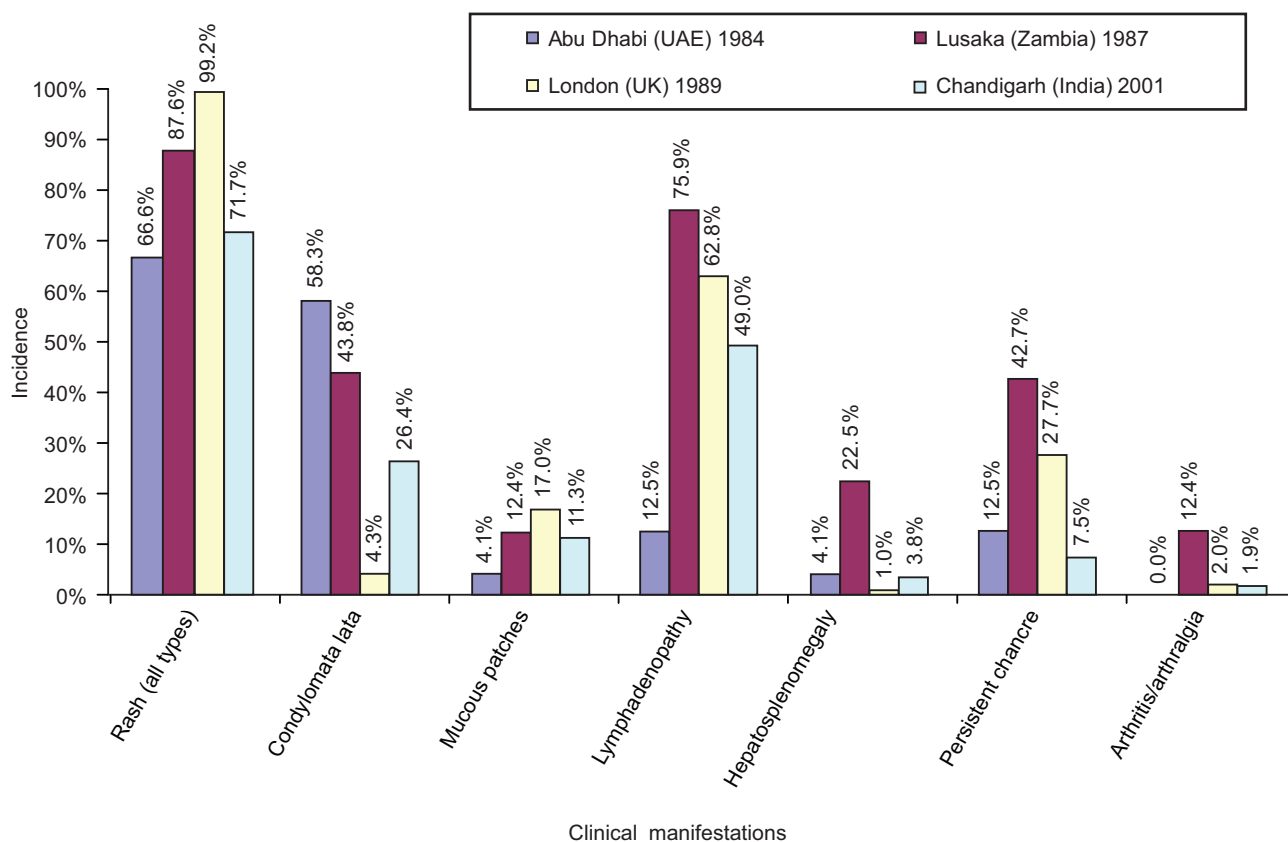
The primary chancre resolves on its own after a period of 2–6 weeks (the average time to healing is 21 days). In about 10% of patients a depressed thin scar is left, which may be an important diagnostic clue in patients presenting with the rash of secondary syphilis. There may be no sharp demarcation between primary



**Fig. 36.8:** Subpreputial discharge due to persistent chancre and rash of secondary syphilis on hands.

and secondary syphilis and in 10–40% patients the chancre may persist even after appearance of the secondary rash (Fig. 36.8).

The clinical manifestations of the secondary stage are protean and can involve any organ.<sup>100</sup> Some patients may develop a flu-like prodrome manifesting as fever, malaise, headache, stiff neck, myalgia, arthralgia, and rhinorrhea. However, skin rash and lymphadenopathy are the most common manifestations of secondary syphilis and are seen in 67–92% and 63–100%, of patients respectively (Fig. 36.9). Although the skin rash is the most common presenting feature of secondary syphilis, as many as 60% of patients with serological



**Fig. 36.9:** Frequency of various manifestations of secondary syphilis in different studies. (From Reference 143).



**Fig. 36.10:** Papular rash of secondary syphilis.

evidence of syphilis do not recall any symptoms or signs suggestive of early syphilis. The rash is often subtle, sometimes consisting of one or two lesions that may pass unnoticed.<sup>101</sup> Although the rash is often described as non-pruritic, 8–42% of the patients complain of some degree of itching.

The rash may be macular, papular, maculopapular (Fig. 36.10), papulosquamous, psoriasiform, annular, pustular, or follicular.<sup>102</sup> Macular or maculopapular rash is the commonest form and seen in about 50% of the patients. Classically, the lesions are described as “raw-ham” or copper colored; however, this characteristic color may be absent in patients with pigmented skin. The rash is usually distributed bilaterally and symmetrically. Macular eruptions, also known as roseola syphilitica, consist of 0.5–2 cm pink, discrete, round to oval, macules distributed over trunk, flexor aspects of the upper extremities and palms and the soles. The face is usually spared. Papular and papulosquamous eruptions evolve from macular lesions. Papules along the hairline on forehead are sometimes arranged in a crown-like pattern that is known as “corona veneris.” Some lesions become scaly and may closely resemble psoriasis and lichen planus. Other morphological variants include follicular, lenticular, corymbose, and annular types. Follicular syphilis is more often associated with pruritus. There is deep dermal tenderness that is elicited by applying pressure with a blunt side of a pin over a papule. This sign is considered pathognomonic for syphilis and is known as the Buschke Ollendorf sign. The resolving rash may leave behind depigmented patches on the back and sides of the neck referred to as leukoderma syphiliticum and described as the “necklace of venus.”

The rash of secondary syphilis has certain characteristics that help to distinguish it from other dermatoses. The rash is generalized, involving both skin and mucous membranes, is



**Fig. 36.11:** Secondary syphilis rash on palms.

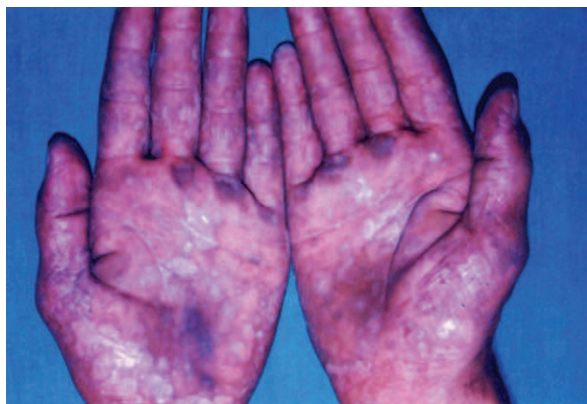
bilateral and symmetrical, and more prominent on the upper extremities than on the abdomen and lower extremities. It has a special predilection for palms and soles (Fig. 36.11). On the trunk it tends to favor lines of cleavage. The lesions are more often discrete than confluent, are sharply demarcated, and have a coppery hue (Fig. 36.12). However, these characteristic lesions are seen more frequently in Caucasians than in Asians and Africans. In Africans, the lesions tend to be confluent (Fig. 36.13), less well-demarcated, and dull red in color.<sup>103</sup>

Although nodular lesions are characteristically seen in late syphilis they have also been described in secondary syphilis.<sup>104</sup> This variant of secondary syphilis is very rare and less than 20



**Fig. 36.12:** Bilateral, symmetrical rash of secondary syphilis. The lesions are discrete and well-demarcated.





**Fig. 36.13:** Confluent lesions of secondary syphilis.



**Fig. 36.14:** Lichenoid rash of secondary syphilis in a HIV-positive woman.

cases have been described in the literature.<sup>105</sup> Histologically, these lesions may show an atypical lymphoid hyperplasia resembling cutaneous lymphoma (pseudolymphoma).

Lichenoid syphilis is characterized by maculopapular lesions with a lichenoid (violaceous) hue (Fig. 36.14). It had been described frequently in the pre-penicillin era. A recent increase in its incidence may be attributable to the HIV epidemic.<sup>106</sup>

The annular syphilid is seen mostly in black patients. It consists of annular lesions on the face, anogenital area, axillae, palms, and soles. The lenticular syphilid manifests as pinhead to lentil or bean-sized papules on face and genitalia.

Corymbose or bombshell-like eruptions are characterized by a central plaque and surrounding smaller satellite papules. This is very rare and usually appears many months after the initial infection.<sup>107</sup>

In warm and moist areas of the body, such as the genitals, perineum, perianal region, under breasts, axilla, and groin, the skin and mucosal lesions of secondary syphilis may proliferate into pale, elevated, moist sharply demarcated papules with flat surfaces. These lesions are known as condylomata lata, (Figs. 36.15 to 36.17) are highly infectious, and are seen in 25–60% of patients with secondary syphilis. At the labial commissures and nasolabial folds, these lesions become elevated and fissured and are called “split papules” (Fig. 36.18).

Mucous membrane involvement is common in secondary syphilis. Mucous patches are a manifestation of the secondary syphilis rash in the oropharynx and at other mucosal sites



**Fig. 36.15:** Condylomata lata in axilla and rash on palm. *Courtesy: Sanjeev Gupta, Kamal Aggarwal, and VK Jain, Rohtak, India.*



**Fig. 36.16:** Condylomata lata on the under-surface of the penis.



**Fig. 36.17:** Perianal condylomata lata in a child with acquired syphilis.



**Fig. 36.18:** Split papules in the nasolabial fold and labial commissures.

(Figs. 36.19 and 36.20). Oropharyngeal infection clinically ranges from asymptomatic inflammation to severe pharyngitis and occurs in 4–17% of cases. Mucosal lesions are in the form of serpiginous ulcers described as “snail track” ulcers, superficial erosions, papules, and plaques. Lesions resembling oral hairy leukoplakia have been described.<sup>108</sup> The oral mucosa, tongue, lips, palate, pharynx, larynx, tonsils, epiglottis, and aryepiglottic folds may be affected.<sup>109</sup> In addition to oropharynx, they can also occur on the genital mucosa. Mucosal lesions on genitalia are more



**Fig. 36.19:** Mucous patch on tongue.



**Fig. 36.20:** Mucous patches on labial mucosa.

common in women because moisture, friction and some irritation favor their development. They may occur on external genitalia as well as on the cervix. All these moist lesions on the skin or mucosa contain numerous treponemes and are highly infectious.

The follicular rash on the scalp may give rise to two patterns of hair loss. Irregular non-scarring patchy alopecia, which is known as “moth-eaten” alopecia (Fig. 36.21), usually occurs at the margins of the scalp or, rarely, in other hairy areas including



**Fig. 36.21:** “Moth-eaten,” patchy alopecia.



the beard, eyebrows, and legs.<sup>110</sup> Telogen effluvium has also been noted in patients with secondary syphilis.<sup>111</sup>

Rarely, involvement of the nail fold or nail matrix by the rash of secondary syphilis results in nail changes, which include pitting, onycholysis, onychodystrophy, and Beau's lines.

Systemic manifestations of secondary syphilis include malaise, fever, mild hepatitis with elevated<sup>127</sup> liver enzymes, iritis, uveitis,<sup>112</sup> arthritis, parotitis,<sup>113</sup> pulmonary changes, and glomerulonephritis. Neurological involvement is common but is often asymptomatic. A study by Rolfs and co-workers demonstrated that *T. pallidum* invades the central nervous system in at least a quarter of the patients with early syphilis regardless of their HIV status.<sup>114</sup> This can be detected on CSF examination, which may show elevated WBC count and proteins and a reactive CSF VDRL. There is more recent evidence that HIV infection (particularly immunosuppression caused by HIV) is associated with a significantly greater rate of CSF changes.<sup>115</sup> Some case reports suggest an accelerated course of syphilis in patients with immunosuppression caused by concurrent HIV infection. These patients appear to have a greater risk of developing CSF abnormalities and asymptomatic neurosyphilis in the second stage of the disease.<sup>116</sup>

Headache is present in up to one-thirds of patients and fever is usually low grade, seldom exceeding 37.8°C.<sup>117</sup> Gastrointestinal symptoms include anorexia, nausea, and occasionally vomiting. Syphilis of the stomach is rare and manifests as mucosal erosions, rugal hypertrophy, or shallow ulcers involving the antral and pyloric area.<sup>118</sup>

Hepatosplenomegaly is reported to occur in 4–23% of patients and jaundice in up to 12% of patients with early syphilis.<sup>100,119</sup> In a study of liver abnormalities in early syphilis, three of 22 patients showed a well-established non-specific reactive hepatitis on histopathological examination. Serum alkaline phosphatase was abnormal in 45% of patients and minimal total hyperbilirubinemia was present in 32% of patients.<sup>120</sup>

Vague bone pain and arthralgia are common but frank arthritis is rarely reported. A retrospective notes review revealed that of 1800 patients with early syphilis, less than 0.2% had evidence of periostitis.<sup>95</sup> Syphilitic periostitis in early syphilis is probably due to vasculitis.<sup>121</sup> Kidney involvement is extremely rare, but asymptomatic proteinuria is well-documented. Other renal manifestations include nephrotic syndrome, rapidly progressive glomerulonephritis, and renal failure.<sup>122</sup>

Cardiovascular complications in secondary syphilis are rare but myocarditis and ventricular arrhythmia in secondary syphilis are well-documented.<sup>123,124</sup>

Lymphadenopathy involving two or more groups is seen in 60–100% of patients. Enlarged lymph nodes are rubbery, painless, discrete, and non-tender. The occipital, axillary, inguinal, and epitrochlear groups of lymph nodes are most commonly involved.

Lues maligna or malignant secondary syphilis is an explosive, widespread form of secondary syphilis that is characterized by a prodrome of fever, headache, and myalgia, followed by a papulo-pustular eruption that rapidly transforms into necrotic,

sharply margined ulcers with hemorrhagic brown crusts that are organized in rupoid layers.<sup>125</sup> The term lues maligna was coined by Bazin and Dubue in the mid 1800s to describe mutilating noduloulcerative variant of secondary syphilis.<sup>126</sup> It was considered to be a common form of syphilis seen during the great epidemic of the 15th century<sup>127</sup> although Cripps et al.<sup>128</sup> found this might not be the case on reviewing the literature. At that time, the characteristic patient with malignant syphilis was described as an alcoholic in poor health who was malnourished and cachectic. These conditions are postulated to cause depression of immunity. Since the turn of the century, there have been only a few reports of lues maligna with just 18 cases described in the English literature. Sixteen of these were men.<sup>126</sup> With the onset of HIV epidemic, several cases of lues maligna in association with HIV infection induced immunosuppression have been reported.<sup>128</sup> Sands et al.<sup>129</sup> reviewed cases of lues maligna reported in the English literature between 1989 and 1994 and found that 11 of 12 cases had concurrent HIV infection. In a multi-centre retrospective study, 7.3% of the patients with secondary syphilis with concurrent HIV infection were found to have ulcerating secondary syphilis, suggesting that this form is 60 times more common in HIV seropositive than in general population.<sup>130</sup> However, recently malignant syphilis has been described in Russia among people with chronic alcohol misuse.<sup>131</sup> Niesser described four clinical characteristics of malignant syphilis<sup>132</sup>: short IP, prodrome, pleomorphic lesions, and noduloulcerative lesions of the skin and mucosae. Mucosal lesions may be milder and in the form of just mucosal patches; however, occasionally widespread atypical oral ulcerations have been reported in lues maligna with concurrent HIV infection.<sup>133</sup>

The onset of lues maligna is characterized by a prodrome of fever, arthralgia, myalgia, headache, and photophobia. Skin lesions start as papules and evolve into pustules; within a few days the lesion centre undergoes necrosis (Figs. 36.22 and 36.23), resulting in sharply margined ulcers with an erythematous halo and a clean looking base.<sup>134</sup> The ulcers are covered with layers of crusts resembling oyster shells (Fig. 36.24). The size of the lesions varies from a few millimeters to several centimeters. In association with HIV, palatal perforation due to lues maligna has been reported.<sup>134</sup>



**Fig. 36.22:** Sharply margined necrotic ulcers with an erythematous halo in malignant syphilis. *Courtesy:* Sanjeev Gupta.



**Fig. 36.23:** Lesions of malignant syphilis on trunk. *Courtesy:* Sanjeev Gupta, Kamal Aggarwal, and VK Jain, Rohtak, India.



**Fig. 36.24:** The ulcers of malignant syphilis, covered with layers of crusts resembling oyster shells.

Criteria for the diagnosis of malignant syphilis proposed by Fisher et al. include compatible gross and microscopic morphology, a high titer of positivity for non-treponemal (RPR/VDRL) tests for syphilis, Jarisch–Herxheimer reaction following treatment, and dramatic response to antibiotic treatment.<sup>124</sup> Reports suggest that florid skin manifestations may be organism-depleted and demonstration of treponemes may not be possible even with sensitive techniques such as immunohistologic methods and Polymerase chain reaction (PCR).<sup>135</sup>

### RELAPSE OF SECONDARY SYPHILIS

The rash of untreated secondary syphilis lasts several weeks to 1 year. However, relapse of secondary syphilis occurs in about 20–25% of patients. The severity of relapsed disease is usually less

than the initial episode. The lesions are fewer in number and smaller in size and, unlike the initial rash, usually asymmetrical. Other rare manifestations include meningovascular neurorecurrence, periostitis, iritis, chorioretinitis, optic neuritis, and hepatitis.<sup>27</sup>

A relapse may be difficult to distinguish from re-infection.<sup>27</sup> But it is likely that the great majority of patients who have clinical or serological relapse of syphilis after standard treatment regimens for syphilis have been re-infected. Evidence of early syphilis in the current sex partner and appearance of a primary chancre at a different location support the possibility of reinfection.

Relapse can be only serological, when in the absence of clinical relapse, the reagin test becomes positive after having been negative, or shows a progressive rise in titers after a decline. This often precedes a clinical relapse. In patients with serological or clinical relapse some clinicians recommend CSF examination to exclude asymptomatic neurorecurrence. Transplacental relapse is defined as birth of a child with syphilis to an apparently cured mother. Infection of a sex partner after an apparent cure can also be evidence of a relapse.<sup>27</sup>

The diagnosis of secondary syphilis is based on positive serology for syphilis. It is also possible to demonstrate *T. pallidum* in mucocutaneous lesions by dark field microscopy. Moist lesions on mucous membranes, which are full of treponemes, are most suitable for this. However, in the mouth, non-pathogenic treponemes are present as part of normal flora and differentiation between them and *T. pallidum* is not easy. Increasingly PCR tests will be used to directly identify *T. pallidum*.

**Differential Diagnosis:** The macular rash of secondary syphilis may mimic rubella, measles, drug rash, glandular fever, and HIV seroconversion illness. A papular or papulosquamous rash may resemble psoriasis (Fig. 36.25), lichen planus, pityriasis rosea, warts, and many other dermatoses.<sup>136</sup> The vesiculopustular rash may be confused with the Von Zumbush type of pustular psoriasis and chicken pox. The differential diagnosis of nodular syphilis includes deep mycoses, leprosy, tuberculosis, sarcoidosis, and lymphoma.<sup>137,138</sup> In the anogenital area, condylomata lata may be mistaken for condylomata acuminata. Syphilitic alopecia may be misdiagnosed as alopecia areata and fungal infection of the scalp.



**Fig. 36.25:** Psoriasiform rash of secondary syphilis.



## EARLY LATENT SYPHILIS

Latent syphilis is defined as positive syphilis serology along with the absence of clinical signs and symptoms. A one year period is considered as the demarcation line between early and late latent syphilis in European (non-UK) and US guidelines and 2 years in the WHO and UK. The distinction between early and late syphilis is important for epidemiological reasons because patients in early latent stage may have relapse of secondary syphilis and thus early latency is considered as an infectious stage. Also, as the duration of infection increases, *T. pallidum* divides more slowly requiring a more prolonged duration of therapy.

Routine screening detects a substantial number of individuals with serologic evidence of syphilis without any previous history of lesions suggestive of primary or secondary syphilis.<sup>139</sup> Incidental use of antibiotics (for other diseases) probably aborts the primary and/or secondary stage(s) of the disease in some of these cases. Asymptomatic acquisition of infection is another possibility, though there is no evidence available to support it. Irrespective of RPR/VDRL titers, these patients should be considered as having late latent syphilis if the duration of the disease is not certain (see also “syphilis incognito” in the chapter on Late Syphilis). Many patients with latent syphilis have cerebrospinal fluid abnormalities suggestive of asymptomatic neurosyphilis; however, it is not clear whether all patients in whom latent syphilis is diagnosed during routine screening should be examined by lumbar puncture to guide therapeutic decisions.<sup>140</sup>

## Histopathology

The histology of the primary chancre is characterized by vascular endothelial cell proliferation and obliteration of the vascular lumen. The proliferation of pericytes is also seen. Intensive cellular infiltration is seen in specimens from older foci. This infiltrate comprises of macrophages, lymphocytes and plasma cells. For descriptive purposes, the infiltrate is classified into four categories: predominantly lymphocytic; lymphohistiocytic; predominantly histiocytic; granulomatous. Plasma cells are present in varying degrees in each category.

Treponemes are visible only by silver impregnation studies, such as the Levaditi or Warthin Starry stains.<sup>141</sup> The epidermis shows acanthosis at the margin of the lesion. Towards the centre the epidermis gradually becomes thinner and appears edematous and there is widening of rete ridges.<sup>142</sup> The ulcer surface is covered with an exudate consisting of fibrin, necrotic tissue, and polymorphonuclear leukocytes.

The predominant inflammatory cell in secondary syphilis is lymphomononuclear and the infiltrate is most intense in the papillary dermis with extension into the deeper dermis. Plasma cells are seen as focal collections around the skin appendages on the periphery of epithelioid cell granulomas (which are seen only in late lesions). However, lesions of condylomata lata show large collections of plasma cells.<sup>143</sup>

The histologic picture in secondary syphilis is not usually specific and may be misleading; it may resemble other common

diseases such as lichen planus and psoriasis. In the rash of secondary syphilis, the epidermis often shows spongiosis, parakeratosis, and acanthosis.<sup>144</sup> Exocytosis is usually seen and cells infiltrating the epidermis are either mononuclear cells or polymorphonuclear leukocytes. Collections of cells resembling Munro abscesses are also seen. In almost all lesions of secondary syphilis, the microvessel count is increased suggestive of angiogenesis.<sup>145</sup> Blood vessels show dilatation, thickening, and an increased number of large endothelial cells. Mural edema and endothelial swelling are commonly seen. A perivascular infiltrate comprising of plasma cells is commonly present. Malignant syphilis lesions may show a picture of vasculitis with fibrinoid material and necrosis of the upper dermis. Follicles and sweat glands may be surrounded by inflammatory cells. In syphilitic alopecia, keratinous plugs and a lymphoid infiltrate are seen around hair follicles.<sup>146</sup>

Treponemes are demonstrable in silver-stained preparations (Warthin Starry stain) in about 70% of the patients.<sup>147</sup> They are usually seen in the epidermis, dermis and around the walls of the capillaries. Immunoperoxidase techniques, using specific polyclonal antibodies against *T. pallidum*, has improved the sensitivity of visualization of spirochetes in paraffin-embedded tissues.<sup>148</sup> The histologic characteristics of syphilitic lymphadenitis include the constellation of follicular hyperplasia, extensive capsular and pericapsular fibrosis with chronic inflammation, sheets of plasma cells, and endarteritis.<sup>149</sup> Isolated giant cells, granulomas, and endothelial hyperplasia are also frequently seen. Silver impregnation stains sometimes detect treponemes in histologic sections from lymph nodes.

## Syphilis and HIV

A significant epidemiological association between infection with *T. pallidum* and HIV transmission has been described in a number of studies and a meta-analysis of 16 early studies estimated that syphilis increased HIV transmission four-fold.<sup>2,150,151</sup> HIV seropositive patients are at a higher risk of having serological evidence of active syphilis, and a similar increase in the serological evidence of HIV is seen with incident syphilis. Primary chancre caused by primary syphilis produces a breach in the continuity of epithelium, giving easy access for HIV to its target cells (CD4+ lymphocytes), which form a significant proportion of the infiltrating cells.

HIV-positive men who have sex with men (MSM) are disproportionately affected by syphilis and in a community-based study, syphilis incidence was almost 10 times higher in HIV-seropositive MSM than in HIV-negative MSM. This difference is largely attributable to behavioral factors and was strongly associated with unprotected anal intercourse.<sup>152</sup>

In HIV and syphilis co-infected patients the CD4 cell count may decline and viral load may increase, which may or may not revert back to baseline levels on successful treatment of syphilis.<sup>153,154</sup>

Syphilis occurring in advanced HIV disease may have atypical features, which are more common in patients with low CD4+ lymphocyte counts as may be expected from a disease where T cell mediated immunity is probably important in immunological

control.<sup>155,156</sup> Although in the majority of syphilis patients co-infected with HIV the clinical manifestations of early syphilis remain unaltered, some may present with unusual features. Healing of primary chancre may be slowed with the ulcer being more often present when secondary infection starts.<sup>84</sup> Primary chancres are more likely to be larger, multiple and painful in HIV-positive individuals.<sup>84</sup> Twenty-one cases of malignant syphilis in association with HIV have been published in medical literature.<sup>157</sup> There are some case series suggesting that a more rapid progression to neurosyphilis may occur<sup>158</sup> and a prospective study suggesting that asymptomatic neurosyphilis is commoner amongst those with HIV.<sup>159</sup> However, it seems that majority of patients have the usual course and manifestations of syphilis and atypical features are seen in only a minority.

Clinical and serological response to conventional treatment for syphilis with penicillin is usually unaltered in patients co-infected with HIV and syphilis.<sup>160,161</sup>

## Syphilis in Pregnancy

Syphilis in pregnancy may result in spontaneous abortion, stillbirth, non-immune hydrops fetalis, intrauterine growth retardation, and perinatal death, as well as serious sequelae in liveborn infected children, such as hepatosplenomegaly, cardiac manifestations, and long-term skeletal and neurological disabilities. Studies from Africa have shown a strong relationship between the incidence of stillbirths, late fetal death and mid-trimester pregnancy miscarriage, and the seroprevalence of syphilis.<sup>162–165</sup> The prevalence of syphilis seroreactivity among pregnant women varies from as low as 0.02% to as high as 12.1% in different parts of the world.<sup>166</sup> Congenital syphilis may occur when an infected woman becomes pregnant or a pregnant woman becomes infected.<sup>167</sup>

The rate of transmission to the foetus in untreated women ranges from 70% to 100% in primary and secondary syphilis, 40% in early latent syphilis, and 10% in presumed late latent syphilis.<sup>61,168</sup> Overall, half of the infants of mothers with untreated syphilis of less than 2 years duration are infected. A higher fetal morbidity and mortality occurs in untreated first trimester and second trimester infection in comparison to third trimester infection, which is more often asymptomatic.<sup>167</sup>

Transmission of syphilis may occur transplacentally to the foetus or during passage through the birth canal by contact of the newborn with a genital lesion. Transmission of syphilis to the foetus is largely dependent on the duration of the disease in the mother; the longer the interval between infection and pregnancy, the more benign is the outcome in the infant (Kassowitz law). However, this law is not absolute and the risk of transmission may be intermittent. Normal offspring may be preceded and followed by an infected infant. Moreover, recent studies have demonstrated that the possibility of fetal infection might never be eliminated and transmission of syphilis to the foetus has been documented up to 10 years after infection.<sup>169</sup> The earlier belief that infection of the foetus does not occur before 18 weeks has been challenged by studies on fetal tissues that have demonstrated

that *T. pallidum* can gain access to the fetal compartment as early as 9–10 weeks.<sup>170–172</sup>

In pregnant women, the primary lesions may be larger, more conspicuous and generally indurated because of increased vascularity in the pelvic tissue. On the cervix, there may be extensive erosions and fissuring, which can heal with a rigid scar which may interfere with dilatation of cervix at parturition.<sup>1</sup>

## Laboratory Diagnosis of Syphilis

As discussed earlier, *T. pallidum* is not an easily cultivable or stainable bacterium. Therefore other laboratory methods to diagnose syphilis in its various stages have been developed. These tests for syphilis have been divided into two broad categories:

### (i) Direct identification of *T. pallidum*:

- Direct microscopic identification of *T. pallidum* is used when lesions are present or when disease is in its early stage before the production of antibodies against *T. pallidum* develops. In this very early stage, diagnosis by serological tests is not possible. This is usually achieved by dark ground microscopy.
- Direct antigen detection tests are used for experimental purposes and in research settings.
- Nucleoside amplification techniques: The PCR is now increasingly used to diagnose syphilis and is considered the gold standard for test evaluation in early syphilis.

### (ii) Serological tests to detect IgG antibodies<sup>173</sup>:

- Non-treponemal tests—to determine disease activity
- Treponemal tests for screening and disease confirmation
- Detection of treponemal IgM antibodies to detect early infection (assays are often combined IgG/IgM tests.)

## DIRECT IDENTIFICATION OF *T. PALLIDUM*

### Dark Field Microscopy

This method is traditionally used to demonstrate *T. pallidum* in the exudate from mucocutaneous lesions in early acquired and early congenital syphilis.<sup>174</sup> This is one of the most specific and easiest methods for diagnosis of infectious syphilis when lesions are present. By this method, primary syphilis can be diagnosed weeks before the appearance of a detectable serological response.

Treponemes cannot be observed with ordinary light microscopy because of their narrow width. In dark field microscopy a dark field condenser allows the light rays to strike the object in the field at an oblique angle so that no direct light, but only light rays that are reflected from the object enter the microscope objective. This gives the object a luminous appearance against a black background.<sup>175,176</sup>

### Specimen Collection

The lesion is cleaned gently with a saline soaked gauze swab and then squeezed with the index finger and thumb to produce a serous exudate. Contamination with blood should be avoided as



it affects the sensitivity of the test. The exudate is then transferred directly to a glass slide by pressing it on the lesion. A drop of normal saline can be added to the exudate to make the material homogenous. The specimen should immediately be examined as any delay reduces the motility of the treponemes.

If there are no mucocutaneous lesions, or the patient has applied antiseptic cream on the chancre, the material can also be obtained by lymph node puncture.<sup>177</sup> The skin over the enlarged lymph node is infiltrated with 1% lidocaine for local anesthesia. The overlying skin is stretched and the lymph node is held firmly. With a disposable syringe, 0.2 mL of sterile normal saline is injected into the lymph node. The lymph node is massaged gently and fluid is aspirated and expressed on a glass slide.<sup>27</sup>

Amniotic fluid obtained by amniocentesis can also be examined by dark field microscopy for treponemes in pregnant women suspected to have early syphilis.<sup>178</sup> Non-pathogenic treponemes are part of normal flora in the oral cavity, therefore dark field microscopy is not recommended for the lesions in the oral cavity.

*T. pallidum* in dark field microscopy is identified from its typical morphology and characteristic movements. Organisms easily confused with *T. pallidum* are *T. refringes*, *T. denticola*, and *T. phagedenis* (Reiter treponeme). They usually do not inhabit the genitalia. *T. pallidum* is distinguished from other treponemes by the tightness of spirals and characteristic corkscrew movements.<sup>173</sup> *T. pallidum* has 6–14 regularly wound coils. The characteristic motion of *T. pallidum* is a slow, deliberate, forward and backward movement, rotation on its long axis, soft bending, and twisting or undulation of the organism from side to side. In contrast, non-pathogenic mucosal treponemes are often irregularly coiled, may be longer and thicker than *T. pallidum*, and lack characteristic motility. *T. pallidum* cannot be differentiated by dark field microscopy from other pathogenic species causing yaws, pinta and endemic syphilis.

However, despite its usefulness as a point-of-care test and its good sensitivity and specificity in expert hands dark ground microscopy has a number of important flaws. It is time consuming, highly dependent on operator experience and training, dependent on well-maintained specialist equipment and its use is therefore confined to specialist centers.

### Direct Fluorescent Antibody– Treponema Pallidum (DFA–TP)

This test is more specific and more sensitive than dark field microscopy and differentiates pathogenic treponemes from non-pathogenic ones. Samples from the oral mucosa can also be examined by this method. Another advantage is that the slides need not be examined immediately and may be sent to a laboratory. However, this test cannot differentiate *T. pallidum subsp. pallidum* from other subspecies of *T. pallidum*. Recently, monoclonal antibody to *T. pallidum* has been used that recognizes an antigenic determinant present only on pathogenic *T. pallidum* but not on non-pathogenic commensal treponemes. The method for sample

collection for DFA-TP is the same as described for dark field microscopy. The slide is air dried and fixed with either acetone for 10 minutes or 100% methanol for 10 seconds. Alternatively, the slide can be heated gently. The smear is stained with fluorescein-labelled anti-*T. pallidum* globulin. After incubation and washing, the slides are examined under the fluorescent microscope. This method can also be used to examine tissue sections of the biopsy from lesions of early syphilis.

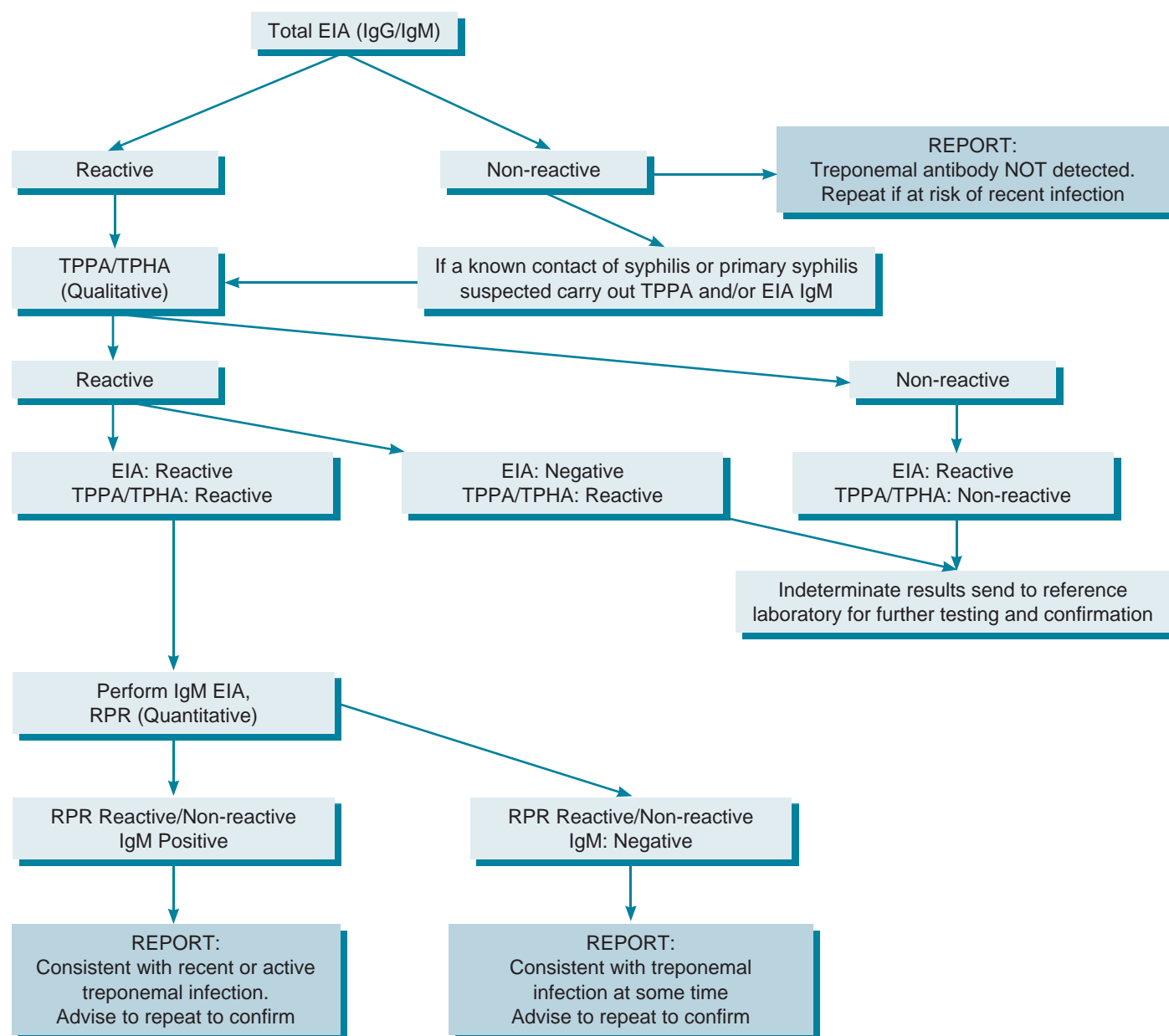
However, despite the utility of this method it is likely that in the future direct identification of *T. pallidum* will be undertaken using nucleoside amplification techniques.

### Polymerase Chain Reaction

The PCR is becoming increasingly established as the investigation of choice for identifying *T. pallidum* from the lesions of early syphilis.<sup>179,180</sup> A number of well-preserved DNA sequences (particularly DNA polymerase gene *polA*) have been identified that are specific for *T. pallidum* and do not appear to be found in other treponemes.<sup>181,182</sup> Assays based on these primers have been shown to be sensitive and specific in the diagnosis of early syphilis and will be increasingly used in the diagnosis of patients presenting with genital ulcers.<sup>182–184</sup> A number of multiplex PCR assays has also been developed for the investigation of genital ulcer disease which allow for the simultaneous detection of *T. pallidum*, *Haemophilus ducreyi* and herpes simplex virus types 1 and 2.<sup>185</sup>

### SEROLOGICAL TESTS FOR SYPHILIS

Unlike most other bacteria, *T. pallidum* cannot be readily sustained in cultures and, in the latent stage of infection, lesions are not present for direct isolation of the pathogen. Therefore serology plays an important role in the diagnosis of *T. pallidum*. *T. pallidum* infection produces antibodies to more than 20 different polypeptide antigens.<sup>186</sup> Specific anti-*T. pallidum* IgM antibodies develop during the second week of infection. IgG antibody response begins around the fourth week after infection and usually persists. Treatment causes a generalized loss of antibodies; however, IgG at a low level usually remains detectable.<sup>186</sup> An ideal serological test should have high sensitivity and specificity. In addition, it should be suitable for treatment monitoring and should give a negative result on successful therapy to allow a clear-cut diagnosis of reinfection. Such an ideal test is not yet available, however by using the different but complementary characteristics of specific and non-specific treponemal tests a diagnosis of syphilis and a serological assessment of disease activity, treatment response and re-infection can be made. Sensitive tests should be used for screening and a positive screening test should always be confirmed by further testing.<sup>187</sup> Treponemal tests are usually used for screening. If resources are available a positive test should be confirmed by a second different treponemal test. A non-treponemal serological test should then be undertaken to assess disease activity and assess treatment response. Fig. 36.26 shows an algorithm for syphilis serology developed by the Health Protection Agency in the UK.



**Fig. 36.26:** HPA testing algorithm.<sup>209,210,214</sup> Adapted from Serological Diagnosis of Syphilis, Standards Unit, Evaluation and Standards Laboratory, 2007. Health Protection Agency, UK.

Rapid, cheap, sensitive and specific point-of-care syphilis tests are becoming increasingly available. These will have a vital role in screening for syphilis in out reach and resource poor environments. At present these are mostly treponemal tests but non-treponemal point-of-care tests are now being developed.<sup>188</sup> The sensitivity of these tests has been found to be high in resource limited clinical settings.<sup>189</sup>

### Treponemal (Specific) Tests

In these tests entire *T. pallidum* or its fragments are used as the antigen to detect antibodies directed against treponemal cellular components. These tests are now increasingly used as

screening tests for syphilis particularly the newer EIA IgG/IgM tests.<sup>190,191</sup>

Treponemal tests become reactive before non-treponemal tests. However, unlike non-treponemal tests, these tests remain reactive for many years (often lifelong) in spite of adequate therapy; therefore, cannot be used for monitoring purposes. False positive results can occur and for that reason an isolated positive EIA or other treponemal test should be treated with caution.

The most commonly used treponemal tests are the EIA tests and the *T. pallidum* particle agglutination assay (TPPA) but tests include the *Treponema pallidum* immobilization (TPI) test, the serum fluorescent treponemal antibody absorption test (FTA-Abs), and the *Treponema pallidum* hemagglutination assay (TPHA).

The development of sensitive and specific enzyme-linked immunosorbent assays (EIA) has been an important development in the diagnosis of syphilis over the past 10 years. Most commercial tests use Nichols strain of *T. pallidum* as antigen. They can be automated, usually become positive within 3 weeks of acquiring syphilis and are becoming increasingly inexpensive. In many parts of the world they are becoming established as the screening test of choice.<sup>192</sup>

The *T. pallidum* immobilization test requires viable virulent *T. pallidum* (Nichols strain) grown in rabbit testes. It is based on the ability of patient antibody and complement to immobilize living treponemes, as observed by dark field microscopy. The test is complicated, technically difficult, time-consuming, expensive, and is now rarely used.

In the fluorescent treponemal antibody absorption test (FTA-Abs) *Treponema pallidum subsp. pallidum* (Nichols strain) is fixed on glass slides. The patient's serum is diluted in an extract from cultures of the non-pathogenic Reiter treponeme to remove non-specific treponemal antibodies, which are present in some individuals in response to non-pathogenic treponemes. This serum is then added to the glass slide. If it contains antibody, it coats the treponemes. Then FITC-labelled anti-human immunoglobulin is added to the slide that combines with the patient's antibody attached to *T. pallidum*. The slide is examined under a fluorescent microscope. Before the development of the more sensitive generation of IgG/IgM EIA tests the FTA-Abs test was the first test to become positive in primary syphilis and had an important role to play in the diagnosis of early disease. However, it is relatively expensive to undertake, cannot be automated, and is prone to false positives when used for screening so is increasingly being relegated to being a confirmatory test used only in cases of diagnostic uncertainty.

The *Treponema pallidum* particle agglutination assay (TPPA), the *Treponema pallidum* hemagglutination (TPHA) test and the microhemagglutination *T. pallidum* test (MHA-TP) test are easier to perform than the FTA-Abs and are suitable for testing a large number of samples. The antigen used in this procedure is ultrasonicated material from the Nichols strain of *T. pallidum* absorbed onto the surface of microparticles (TPPA) or formalinized, tanned sheep erythrocytes (TPHA, MHA-TP). As in the FTA-Abs test, the patient's serum is first diluted in sorbent to remove non-specific treponemal antibodies. The serum is then placed in a microtiter plate and if antibodies are present in the serum, they react with the particles or sheep erythrocytes to agglutinate them.

Reactive results are shown by an agglutinated particle spot or smooth mat of cells covering the entire bottom of a well. Non-reactive results show a definite compact red button in the centre of the well, with or without a very small hole in the centre. The TPPA is increasingly used as the treponemal test of choice to confirm positive EIA tests as it is easier to automate and becomes positive earlier in the course of primary infection. It is almost always positive before the VDRL/RPR test.<sup>191</sup>

Detection of Treponemal IgM Antibodies is used by some clinicians to diagnose early infection and assess disease activity.

However, the emergence of combined IgG/IgM screening tests is reducing their utility in routine practice. IgM antibodies against *T. pallidum* appear in serum toward the end of the second week of infection, about 2 weeks before the detectable IgG response. Unlike the IgG antibody response, which persists years after adequate treatment, the IgM antibodies decline gradually and disappear usually within 6 months (range: 3–24 months, depending on the stage of infection). Thus specific IgM antibodies have been considered as indicators of active syphilis. Detection of IgM antibodies is of great diagnostic significance when congenital syphilis is suspected and may be useful if reinfection is being considered.<sup>174</sup> The molecular size of IgM prevents it from passing the placental and blood-brain barriers, while IgG antibodies freely cross these two barriers. Therefore, presence of IgG antibody in the newborn or in CSF may not be an indicator of congenital syphilis or neurosyphilis, respectively, while presence of specific IgM indicates an active infection.

Increasingly combined IgG/IgM EIA tests are being used for syphilis screening.

### Non-treponemal (Non-specific) Tests

The two most commonly available non-treponemal tests are the Venereal Disease Research Laboratory (VDRL) test and Rapid Plasma Reagin (RPR) test. Both tests have the same standardized antigen comprising of lecithin, cholesterol, and purified cardiolipin (a component of mammalian cell membranes) to detect antibody against cardiolipin. The tests have similar sensitivity and specificity but the RPR is becoming increasingly used because of the wider availability of reagents and simpler reading protocol.

The VDRL slide test has to be read using a microscope. The test is performed on serum heated at 56°C for 30 minutes. Serum and antigen are mixed within a ring on a glass slide by rotating it mechanically and results are read in a microscope at 100× magnification. If anticardiolipin antibodies are present, the antigen rods aggregate to form clumps. A quantitative test can be performed using serial dilutions of the serum.

RPR test can be read visually (macroscopically) because of the presence of a colored substance in the antigen preparation. It is performed on plastic coated cards onto which circles have been imprinted. Standardized amounts of undiluted serum and stabilized antigen suspension containing charcoal particles are mixed within the circles and spread over it.<sup>187</sup> To perform quantitatively, serially diluted serum is mixed with the antigen. The card is rotated at 100 rpm for 8 minutes. Presence of anticardiolipin antibodies produces flocculation of charcoal particles, which is classified as a positive test. The RPR test has several advantages over VDRL. It can be read macroscopically because of addition of charcoal particles, the antigen used is stabilized and cards are used instead of slides.

The RPR teardrop test is a refinement of the RPR test developed for use as a screening procedure in the field, while the RPR card circle test is used in laboratories for testing large number of specimens.<sup>173</sup> Another modification of the RPR, the

**Table 36.1:** Summary of the Course and Stages of Sexually Acquired Syphilis

Infectiousness	Stages	Time, post-infection	Clinical presentations
Early or infectious syphilis	Primary	9–90 days; average 3–4 weeks	Single or multiple, painless, indurated chancre(s) at the site of inoculation
	Secondary	Few weeks to 6 average months. 6–7 weeks	Rash, fever, malaise, lymphadenopathy, condylomata lata, mucous lesions, patchy alopecia, meningitis, headache
	Early latent	≤1 year	Asymptomatic
Late or non-infectious syphilis	Late latent	>1 year	Asymptomatic
	Late benign—gumma	1–46 years, average 10–15 year;	Gummatous lesions of any organ—liver, eyes, stomach, lungs, and testes
	Cardiovascular	10–30 years	Aortic aneurysm, aortic regurgitation, coronary artery ostial stenosis
	Neurosyphilis		
	Asymptomatic	None	
	Acute syphilitic meningitis	<2 years	Headache, meningeal irritation, confusion
	Meningovascular syphilis	5–12 years	Headache, vertigo, cranial nerve palsies, acute vascular events with focal findings, personality disturbances
	General paresis	15–20 year	Insidious changes in personality and behavior, insidious onset with dementia, delusional state, fatigue, intention tremors, loss of tone of facial muscles
	Tabes dorsalis	20–25 years	Lightening pains, dysuria, ataxia, Argyll Robertson pupil, areflexia, loss of proprioception, Charcot joints

toluidine red unheated serum test (TRUST), uses paint pigment toner toluidine red particles in place of charcoal particles.<sup>172</sup> An indirect enzyme-linked immunosorbent assay (ELISA) test has also been introduced using the VDRL test antigen.<sup>173</sup>

As the antigen used in non-treponemal tests is a component of all mammalian cell membranes, the damage to tissues caused by infection, immunization, pregnancy, age-related changes, or autoimmune diseases can result into false positive non-treponemal test results.<sup>18,193–196</sup> The reactivity in such cases is usually only in low dilutions (<1:8); however, in exceptional cases, false reactivity in very high titers (up to 1:256) has been reported.<sup>195</sup> The false reactivity can be acute (of <6 months duration) or chronic (of >6 months duration) (see Table 36.1).

However, as treponemal tests are increasingly used for syphilis screening an isolated positive non-treponemal test is becoming more unusual.

The prozone phenomenon is an immunological event seen with non-treponemal tests, which are based on antigen-antibody interaction. An agglutination or precipitation reaction will be positive depending on several factors that determine the size and solubility of the immune complexes formed *in vitro*. The optimal ratio of antigen to antibody yields an insoluble precipitate that is visible in a positive test. The “zone of equivalence” defines this optimal ratio. In the zone of antibody or antigen excess (prozone and postzone, respectively), false negative test results will occur.<sup>197</sup> It is present in 1% to 2% of serum samples from patients with syphilis and is unusual in non-HIV seropositive patients with syphilis, ranging from 0% to 0.4%. False negative non-treponemal tests can occur in patients with titers <1:4 dilutions, if the blood samples are stored at a cold temperature (4°C) before testing. An appropriate temperature for storage of blood samples is 27°C.

## Laboratory Diagnosis of Syphilis in Various Stages

### PRIMARY SYPHILIS

A presumptive diagnosis of primary syphilis is based on the presence of a chancre and a preceding history of sexual contact within the last 3 months. In early stages, when serology is still negative, detection of treponemes in the serous exudate from the chancre by dark field microscopy or PCR or DFA–TP confirms the diagnosis.

Humoral antibody response to *T. pallidum* is detectable by non-treponemal or treponemal serological tests only 1–4 weeks after the chancre has formed and non-treponemal tests (RPR/VDRL) have a sensitivity of 70–90% in primary syphilis. The combined IgG/IgM tests have a reported sensitivity in primary syphilis of up to 96% and the TPPA is reported to have sensitivity of up to 94% in primary syphilis.<sup>190,191</sup>

### SECONDARY SYPHILIS

All serological tests are positive at this stage and sensitivity for all tests approaches 100%; however, in 1–2% of patients, false negative non-treponemal tests can occur due to prozone phenomenon (see above). A presumptive diagnosis is based on the presence of typical rash and reactive non-treponemal tests in a titer greater than 1:8 in a patient with no previous history of syphilis. If a past history of syphilis is present then the criteria should be a four-fold rise in the titer. When the titer of non-treponemal tests is less than 1:8, the test should be repeated and a treponemal test should also be performed. Reactivity in dual testing (both non-treponemal and treponemal) is confirmatory.



Treponemes can be identified in lesions by dark field microscopy or PCR and that is also confirmatory.

### LATENT SYPHILIS

As the lesions are not present in latent syphilis, the treponemes cannot be detected for a definitive diagnosis. All serological tests are reactive in early latency. However, the reactivity to non-treponemal tests decreases with the increasing duration of latency, and in approximately 30% patients with late latent or late syphilis, VDRL/RPR tests are negative.<sup>186</sup> The sensitivity of treponemal tests in late latent syphilis varies from 97% to 100%. Most of the patients with latent syphilis are diagnosed presumptively on the basis of reactive syphilis serology during screening.

### Serological Tests for Screening

At most centres, the screening for syphilis is a two step process; first, testing serum with a treponemal test (usually an EIA test) and second, confirming reactive samples with a second treponemal test (usually a TPPA or TPHA test) and undertaking non-treponemal (RPR or VDRL) testing. A modified UK testing algorithm is shown in Fig. 36.26.

In resource-limited settings, the RPR remains a useful test for screening as it is easy to perform, inexpensive and less resource intensive. It can also provide a point-of-care test result.

Routine screening for syphilis is done in many settings, for example, pregnant women, HIV clinic attendees, hospitalized patients, STI clinic attendees and blood and tissue donation.

In many countries, six-monthly syphilis serology is included in the monitoring of HIV seropositive individuals.<sup>198</sup> In areas with an outbreak of syphilis, an increased surveillance in HIV infected persons at 3-month intervals is recommended to detect syphilis at an earlier stage. This reduces the duration of infectiousness.<sup>199</sup>

In most countries, routine antenatal screening for syphilis is recommended to prevent congenital syphilis. As the transmission to the foetus usually takes place at 4 months of gestation, early antenatal serological screening and treatment prevents most cases.<sup>200–202</sup> The WHO has recommended that serological screening tests should be performed on all pregnant women at their first antenatal care visit and this should be repeated early in the third trimester. In areas with a high prevalence of syphilis, the CDC in the US has recommended re-screening in the third trimester and again at the time of delivery to detect new infections during pregnancy. In one study from South Africa, seroconversion rate for syphilis at the time of delivery was 2.7%.<sup>203</sup> Transmission to the foetus from mothers who acquire syphilis during pregnancy is almost certain and can only be recognized by repeat screening in the third trimester.<sup>204</sup>

### Treatment

The primary goals of therapy are to prevent transmission and avoid late complications of syphilis.<sup>18</sup> To achieve these, a therapeutic level of antimicrobials needs to be achieved in the serum and in the CSF if there is clinical evidence of CNS involvement.

**Table 36.2:** The Standard Treatment Recommendations for Infectious Syphilis<sup>13,16,191–194</sup>

Stage	Standard treatment	Alternatives
Primary, secondary, and early latent syphilis	Benzathine penicillin 2.4 mega units intramuscularly as a single dose or aqueous procaine penicillin 600,000 units intramuscularly per day for 10 days	Doxycycline 100 mg orally twice a day for 14 days
Late latent syphilis	Benzathine penicillin 2.4 mega units intramuscularly weekly over two weeks (three injections days 0,7,14) or Aqueous procaine penicillin 900,000 units intramuscularly per day for 17 days	Doxycycline 100 mg orally twice a day for 28 days
Neurosyphilis	Aqueous procaine penicillin 1.8–2.4 mega units intramuscularly per day for 17 days combined with probenecid 500 mg four times per day or intravenous benzylpenicillin 3–4 MIU 4 hourly for 14 days	Doxycycline 200 mg orally twice daily for 28 days

The standard treatment recommendations for infectious syphilis and the recommendations for complicated early syphilis and early syphilis in pregnancy are shown in Table 36.2.<sup>16,19,205–208</sup>

### PENICILLIN

Parenteral penicillin therapy remains the cornerstone of syphilis treatment and is the only treatment for which long-term follow-up data is available.<sup>1,201,203,208</sup>

A serum level of penicillin greater than 0.018 mg/L is considered as treponemocidal and in early syphilis *T. pallidum* divides every 30–33 hours.<sup>206,207</sup> Therefore a therapeutic level of penicillin maintained for 7–10 days is considered sufficient for curative treatment. In late syphilis, treponemes divide more slowly as supported by the studies that show the persistence of viable treponemes in lymph nodes of patients with latent syphilis and experimentally infected rabbits after doses of penicillin that are curative for early syphilis.<sup>206,207</sup> Therefore the therapeutic levels of penicillin in serum are required for a much longer duration in late syphilis than that are required for early syphilis.<sup>208</sup> Penicillin G is the drug of choice for all stages of syphilis. Parenterally administered penicillin G is preferred as it provides guaranteed bioavailability and is a directly observed therapy (DOT).<sup>209,210</sup> In general a depot preparation of a long-acting penicillin is preferred for the treatment of syphilis because they are easy to administer, are inexpensive, and do not require frequent re-administration.<sup>18</sup> Benzathine penicillin offers an effective and simplified treatment. Its blood levels remain persistent at a low, but treponemocidal, level for 18–25 days. Its reconstitution with lidocaine reduces the discomfort associated with injection.<sup>168</sup>

The concentration of penicillin in CSF is less than 10% of that of the serum level. Mohr et al.<sup>211</sup> found that 12 of 12

patients treated with benzathine penicillin had no detectable penicillin<sup>212</sup> in the CSF. Tramont reported isolation of *T. pallidum* from the CSF of two asymptomatic adult patients treated with recommended doses of penicillin. CSF abnormalities have been detected in nearly 30% of patients with primary and secondary syphilis.<sup>213</sup> None of the intramuscular penicillin treatment regimens consistently produce treponemicidal concentrations in CSF. However, there is no evidence that in patients with early syphilis, persistent treponemes in the CNS after benzathine penicillin G therapy cause relapse. Thus a single injection of benzathine penicillin remains the treatment of choice for all patients with early syphilis despite evidence of early invasion of the CNS by *T. pallidum* in some patients.<sup>159,114</sup>

Failure to cure early syphilis with recommended doses of penicillin has been reported.<sup>215,216</sup> However, in these cases the extended re-treatment with penicillin resulted in cure, so it was not considered that treponemes were less sensitive or resistant to penicillin. Nevertheless, treatment failure with penicillin in early syphilis is extremely rare and it gives a cure rate of nearly 100% in primary and secondary syphilis.<sup>217–219</sup>

A serum amoxicillin concentration of 0.11 g/L was established as being treponemicidal in a rabbit model with orchitis. Seventeen patients treated with amoxicillin 3 g twice a day and probenecid 0.5 g twice a day given for 3 weeks has been found to be a good alternative to injectable penicillin in HIV infected patients with syphilis, as it achieves a high concentration in the CSF. However, the gastrointestinal side effects are troublesome and many patients may not complete the therapy.<sup>220</sup> Rolfs et al. compared the efficacy of a single injection of benzathine penicillin 2.4 million units with enhanced therapy comprising of a combination of a single injection of benzathine penicillin plus 2 g of amoxicillin and 500 mg of probenecid taken orally 3 times daily for 10 days in patients with primary and secondary syphilis.<sup>114</sup> They found that enhanced therapy with amoxicillin and probenecid did not improve the outcome. In a study on the efficacy of amoxicillin in 89 patients with syphilis who were HIV seronegative, the cure rates were 100% for primary and secondary syphilis, 66.7% for late syphilis, and 60% for adult congenital syphilis.<sup>221</sup>

## Allergic Reactions to Penicillin

The main hazard treatment of syphilis with penicillin is allergic reactions, most serious of which are angioedema and anaphylaxis (Type I hypersensitivity). Angioedema manifests as marked swelling of the lips, tongue, face, and periorbital tissues with or without bronchospasm and skin rash.<sup>222</sup> The clinical picture in anaphylaxis varies widely in severity but can be associated with circulatory collapse, severe hypotension, and death. In less dramatic cases, bronchoconstriction with abdominal pain, nausea, vomiting, diarrhea, extreme weakness, fall in blood pressure, and purpuric skin rash can occur in various combinations. The incidence of anaphylaxis/angioedema varies from 0.04% to 0.2% in persons treated with penicillin. However, death following these reactions is extremely rare and is estimated to be approximately 0.001%.<sup>222</sup>

A reliable history of previous adverse response to penicillin is valuable in predicting whether a patient will have an allergic reaction. A specific history for various manifestations of immediate hypersensitivity reactions, like urticaria, angioedema, anaphylactic shock, and maculopapular rash may be taken. However, the condition is over-diagnosed on the basis of history alone.<sup>222</sup>

An intradermal test for penicillin allergy may be performed using standard amounts of a mixture of a major determinant (benzylpenicilloyl polylysine) and minor determinants, e.g. benzylpenicillin itself. A positive reaction is defined as appearance of a flare and wheal reaction greater than 3 mm or more in diameter. Only about 10% of patients with a history of “penicillin allergy” show a positive reaction to intradermal test, which suggests that many who are so labeled are not, or are no longer, allergic to penicillin.<sup>223</sup> The risk of an acute systemic allergic reaction to penicillin in a person with positive skin tests is approximately 67%.<sup>224</sup> Risk of anaphylactic reaction is more in patients reactive to minor determinants than in those reactive to major determinants alone. Unfortunately it is difficult to obtain the major and minor determinants of allergy commercially and in practice penicillin allergy is usually diagnosed on history alone.<sup>178</sup>

## Desensitization to Penicillin

Patients who report penicillin allergy are usually treated with alternative antibiotics.<sup>225</sup> However, in some instances the alternative therapies are unacceptable, for example, doxycycline in pregnancy. Alternative antibiotics may also be less effective than penicillin, for example syphilis in pregnancy and in neurosyphilis, some alternative drugs (particularly macrolides) may not cross the placental and blood–brain barriers in sufficient amounts to achieve treponemicidal concentration. In such patients desensitization is recommended. This procedure consists of administering gradually increasing doses of penicillin. This results in a subclinical anaphylactic discharge and binding of all IgE, and a state of antigen-specific mast cell unresponsiveness is achieved before full doses are administered. The desensitization process can be done through the oral route or intravenous route. The former is preferred and standard desensitization protocols are illustrated in Table 36.3. It is recommended that desensitization is repeated if further courses of penicillin therapy are required.

## Management of Reactions to Penicillin

All patients receiving penicillin should be advised to stay for observation for at least 20 minutes. If an anaphylactic reaction is suspected, rapid assessment and treatment is essential. Patients with anaphylaxis require intravenous adrenaline followed by parenteral antihistamines and corticosteroids. Some individuals will require cardiopulmonary resuscitation with a particular need to maintain airway.

## Procaine Reaction

Inadvertent intravenous injection of procaine penicillin may result in the procaine reaction (also known as Hoigne syndrome

**Table 36.3:** Causes of False-positive Serological Tests for Syphilis; Listed in Alphabetical Order.<sup>13,37,189,191,218-221</sup>

Infectious causes			Non -infectious causes
Bacterial	Viral	Parasitic	
Bacterial endocarditis	Chickenpox	Malaria	Advanced cancer
Chancroid	HIV	Trypanosomiasis	Chronic liver disease
Leprosy	Infectious mononucleosis		Connective tissue disease
Leptospirosis	Measles		Intravenous drug use
Lymphogranuloma venereum	Mumps		Lymphosarcoma
<i>Mycoplasma pneumoniae</i>	Vaccinia		Multiple blood transfusions
Psittacosis	Viral hepatitis		Multiple myeloma
Relapsing fever			Old age
Rickettsial disease			Pregnancy
Scarlet fever			
Tuberculosis			

or procaine psychosis.) It occurs just after or even during administration of procaine penicillin. It is a short-lived reaction whose hallmark is a sense of “impending doom.” It usually only lasts 15–20 minutes and usually all that is required is calm reassurance. Occasionally, the patient will need resuscitation if this syndrome is associated with circulatory collapse.

## Jarisch–Herxheimer Reaction

Management of Jarisch–Herxheimer reaction has been described below.

## CEPHALOSPORINS—CEFTRIAZONE

Although there is a 10–20% cross-hypersensitivity risk for patients treated with cephalosporins who are allergic to penicillin some clinicians do recommend this therapy in patients with a history of penicillin allergy. Treatment with intramuscular ceftriaxone in early syphilis appears to be effective, but it has to be given for 5–10 days. Single dose of ceftriaxone is insufficient for cure.<sup>214</sup> Ceftriaxone has been found to be effective in patients with latent syphilis and neurosyphilis with and without HIV infection.<sup>226–229</sup> It has been shown to have good CNS penetration. The treponemicidal concentration for ceftriaxone is 0.0006 mg/ml. and levels well above this can be achieved in CSF by giving 1 g daily, although, most guidelines recommend a dose of 2 g daily if neurosyphilis is suspected. Ceftriaxone is preferred over other cephalosporins because of its longer half-life of 7 hours.<sup>227,229</sup> The drug is best given by intravenous route, as intramuscular ceftriaxone may not be an adequate treatment for neurosyphilis. Lower intramuscular doses may be given for early syphilis.

## MACROLIDES

### Erythromycin

Treatment regimens with erythromycin have not been evaluated extensively in early or late syphilis. Erythromycin has been recommended as an alternative drug for patients allergic to penicillin or for those who refuse parenteral therapy. The efficacy also depends on the compliance of the patients.

In pregnant women with early syphilis, erythromycin gives sub-optimal success rates in prevention of congenital syphilis.<sup>230</sup> There are reports of failure of erythromycin therapy in HIV infected patients with early syphilis.<sup>231</sup>

### Azithromycin

Azithromycin is a long-acting, azalide antimicrobial agent. It has a long half-life (68 hours) and can be given orally. Oral administration of azithromycin results in low but prolonged plasma levels, high intracellular concentration, and high concentrations in most tissues, including CNS.<sup>232</sup> In experimental studies, azithromycin has been found to be active *in vitro* against *T. pallidum*<sup>233</sup> as well as effective in treating syphilis in rabbits.<sup>234</sup> This has led to several studies of its use in treating patients with syphilis. In open studies, single daily doses of 500 mg azithromycin given for 7–10 days was found to be effective treatment for primary and secondary syphilis. A single dose of azithromycin 1 g has been found to be effective in the treatment of incubating syphilis in persons exposed to partners with infectious syphilis.<sup>235</sup>

A single randomized trial of azithromycin 2 g given orally as a single dose compared to single dose Benzathine penicillin for early syphilis showed good azithromycin efficacy.<sup>236</sup> However, although azithromycin as a single dose oral therapy is an attractive therapy it has not become established as a first line treatment as treatment failure is well-recognized and some strains of syphilis are intrinsically resistant to macrolide therapy due to a A2058G mutation in the 23S ribosomal RNA (rRNA) gene of *Treponema pallidum*.<sup>237,238</sup> This mutation has not been found in specimens from Madagascar.<sup>239</sup> At present azithromycin cannot be recommended in the first line of therapy in syphilis except in Sub-Saharan Africa.<sup>240</sup>

## TETRACYCLINES

Long-acting oral tetracyclines are recommended for patients with early syphilis. Tetracycline in a total dose of 24–32 g given over a period of two weeks is effective in the treatment of early syphilis. However, the drug is given orally and its efficiency depends on the compliance of the patient.

Doxycycline, 200 mg daily, orally, in two divided doses is equally effective.

Doxycycline has several advantages over traditional tetracycline. It is better absorbed, can be taken with food, requires less frequent dosing because of its longer half-life, and has better penetration to CNS because of its high lipid-solubility.<sup>241</sup> There are occasional reports of relapse in patients with early syphilis treated with adequate doses of doxycycline; however, a possibility



of reinfection could not be excluded in such patients.

A large retrospective comparative study of doxycycline 100 mg twice daily versus single dose Benzathine in the treatment of early syphilis in HIV positive<sup>242</sup> individuals showed similar efficacy in the two regimes. Doxycycline crosses the blood-brain barrier and sufficient concentration is obtained in CSF.<sup>241</sup> Tetracyclines are contraindicated in pregnancy.

### TREATMENT IN PREGNANT WOMEN

In one study, single injection of benzathine penicillin 2.4 million units showed a 98% success rate in preventing congenital syphilis in pregnant women with early syphilis and introducing an intervention of antenatal screening and single dose Benzathine penicillin has been shown to eliminate all the adverse consequences of syphilis in pregnancy.<sup>202</sup> However, the success rates in other studies have been lower than this, particularly for women treated for syphilis in the last trimester and therefore some clinicians recommend that all pregnant women with early syphilis should be treated with two injections of benzathine penicillin (2.4 million units) given one week apart.<sup>243</sup> Pregnant women with syphilis of unknown duration and late syphilis should receive three injections of Benzathine penicillin one week apart over two weeks (day 0, 7, and 14) or a 15-day course of aqueous procaine penicillin (600,000 units IM) once daily.

### TREATMENT IN HIV-POSITIVE PERSONS

There have been some reports of progression to neurosyphilis after adequate therapy of patients with early syphilis who are also co-infected with HIV.<sup>243–245</sup> This has prompted some experts to recommend CSF examination of HIV-infected patients with early syphilis at the time of presentation. These experts recommend that all such patients with CSF abnormalities should be treated for neurosyphilis. However, the results of CSF examination are difficult to interpret in HIV seropositive persons as they have a high rate of CSF abnormalities unrelated to syphilis.<sup>246</sup> Respondents of a survey of Infectious Disease experts revealed that those who treated more patients with syphilis were less likely than those who treated fewer patients with syphilis to perform a lumbar puncture for an HIV-positive patient co-infected with secondary syphilis without neurologic or ophthalmologic symptoms. Authors of the survey concluded that these findings suggest that increased experience managing syphilis may correlate with confidence that management according to established guidelines is sufficient to prevent adverse outcomes.<sup>247</sup> As discussed earlier, augmented therapy with amoxicillin and probenecid has not been found superior to the conventional therapy in these patients.<sup>114</sup> No consistent data are available on either frequency of treatment failures or of progression to neurosyphilis and other complications.<sup>248</sup> Contradictory reports exist on serological response to conventional treatment of syphilis in HIV seropositive patients, with some studies showing a similar serological response for syphilis in HIV negative and HIV positive patients, while others show a delayed or absent serological improvement in HIV

positive patients.<sup>161,246</sup> Therefore, all major treatment guidelines recommend the same treatment for patients with all stages of syphilis with HIV infection as that for patients with syphilis without concurrent HIV infection.<sup>16,19,205</sup> However, a more frequent serological and clinical follow-up (at 3, 6, 9, 12, and 24 months post-treatment) has been recommended for these patients. If during the follow-up, any patient shows a rise in the titers or relapse of signs and symptoms, then some guidelines recommend that CSF should be examined and re-treatment should be guided by the results of the CSF examination.

Likewise, some guidelines recommend that all HIV seropositive patients with late latent syphilis or latent syphilis of unknown duration should undergo CSF examination. Those with no CSF abnormalities should be treated with three injections of benzathine penicillin 2.4 million units given one week apart. US guidelines suggest that patients with CSF abnormalities need to be treated for neurosyphilis.<sup>19</sup> Some experts also recommend CSF examination 2 years after treatment of early syphilis in all HIV seropositive patients.<sup>16</sup> However, these recommendations are not supported by clinical trial evidence.

### JARISCH–HERXHEIMER (J–H) REACTION

The J–H reaction is a febrile illness that occurs within the first 24 hours of antimicrobial treatment and is commonly seen in patients with early infectious syphilis. The reaction is associated with increased circulating levels of tumor necrosis factor alpha (TNF-alpha), interleukin-6 and interleukin-8. Lysis of spirochaetes, releasing endotoxins probably contributes in its pathogenesis.

In various studies, the J–H reaction has been observed in 18.8–95% of patients with early syphilis.<sup>248–250</sup>

The J–H reaction occurs as an acute febrile illness with rigors, headache, myalgia, and rash of secondary syphilis appearing or becoming more prominent. It usually occurs between 3 and 12 hours after treatment. The reaction is important in pregnant women with syphilis in whom it may induce early labor or cause fetal distress, which however, should not prevent or delay the therapy.<sup>205</sup> A prospective study of 33 pregnant women treated with penicillin for early stage syphilis showed that most women experienced self-limited uterine contractions, decreased fetal activity, and fetal heart rate abnormalities, however there were no events of premature labor.<sup>251</sup> Complications due to J–H reaction have also been described in neurosyphilis, ocular syphilis, cardiovascular syphilis, and syphilis of the larynx because of the local edema. Because of these potential complications, some recommend a small dose of glucocorticoids (10–20 mg prednisolone) started one day before specific therapy instituted in patients with late syphilis involving CNS, heart or larynx, however, its effectiveness has never been proved. In such patients, treatment with a TNF-alpha antagonist may be more effective in suppression of inflammation and prevention of tissue destruction although the evidence for its use is currently lacking.<sup>248</sup>

Patients who are being treated for early syphilis should be warned about the possibility of the J–H reaction and should



be advised to rest take antipyretics and drink clear fluids until symptoms settle.

## MANAGEMENT OF SEX PARTNERS

CDC recommends presumptive treatment for all sex partners exposed during last 90 days irrespective of their serological status, considering that these contacts may have incubating syphilis.<sup>205</sup>

Sex partners exposed more than 90 days before should be screened and managed according to their serological status. If serology is not immediately available, then all such contacts should also be treated epidemiologically.

The treatment of choice for epidemiological treatment of syphilis is a single dose of Benzathine penicillin 2.4 MIU intramuscularly. It is likely that doxycycline 100mg twice daily for 14 days is effective for treating incubating syphilis and there is evidence that Azithromycin 1 g as a single dose is a useful treatment to prevent incubating syphilis.

## SEROLOGIC RESPONSE TO SYPHILIS TREATMENT

Patients with clinical manifestations of early syphilis (ulcers, rash, etc.) should be followed up to ensure that these have resolved with treatment. There is no ideal test of cure for syphilis available that can be carried out within days or weeks after treatment. The great majority of patients treated with standard penicillin and doxycycline based regimes for early syphilis are cured with most clinical and serological relapses being caused by re-exposure to syphilis. Patients can be re-assured that they have cured provided that therapy is fully adhered to. The goals of serological follow-up are to confirm treatment response, identify re-exposure and establish the post-treatment RPR/VDRL level from which re-infection can be determined.

In most guidelines a four-fold (two titer) RPR/VDRL titer fall by six months or earlier after treatment of early syphilis is considered an adequate treatment response.

To assess treatment, the patient is asked to return for repeat quantitative non-treponemal serologic testing (VDRL/RPR) and at 3, 6 and 12 months. When the serologic test becomes negative the patient can be discharged from care. Generally seroreversion is achieved in the majority of the patients with primary syphilis in about 12 months after treatment<sup>217</sup> and in those with secondary syphilis in about 24 months.<sup>218</sup> Talwar et al. found that at 30 months post treatment, only about 6% patients with primary syphilis and 8% patients with secondary syphilis were seroreactive.<sup>252</sup> The seroreversion is more rapid after therapy if the duration of infection is short and if the initial titer is low. Romanowski et al. observed that more than 80% patients with primary syphilis with pre-treatment titer less than 1:8 were seroreverted at 24 months, while only 20% of those with pre-treatment titer greater than 1:256 were seroreverted after that period.<sup>253</sup> For patients with secondary syphilis, these figures were 60% and 8%, respectively and those for early latent syphilis, 31% and

0%, respectively.<sup>253</sup> However, the rate of decline of high titer reactivity is more rapid after treatment than the rate of decline of lower titer reactivity.<sup>236</sup> Seroreversion may be delayed in repeat infection. As seroreversion is a slow process requiring months to years, the rate of decline is a better indicator of therapeutic response. A 4 fold (two titer) decline in the titer is considered a good therapeutic response and this should occur within 3 to 6 months after therapy in patients with primary and secondary syphilis and within 12 months in early latent syphilis. VDRL titers may not decline in patients with late syphilis and remain reactive at a low level (<1:8) for many years after adequate treatment.<sup>253</sup> There is no satisfactory monitoring test available for non-treponemal tests-negative late disease.<sup>173</sup> Patients with syphilis who are HIV positive may show less serological improvement after conventional treatment than patients with syphilis who are HIV negative. The interval between treatment and a fourfold decrease in titer may be longer in HIV positive patients than in HIV negative patients.<sup>246</sup> This difference is more pronounced in patients with pre-treatment titers of 1:32 or less.

The treponemal tests are less likely to serorevert. In one study, it was observed that treponemal tests seroreverted only in 10–15% of patients with a first episode of primary syphilis, but in none of those with latent syphilis at 24 months after adequate treatment.<sup>252</sup>

## Prevention and Control

Conventional public health methods of enhanced surveillance, screening, partner notification, as well as collaboration with community-based non-governmental organizations are important in the control and elimination of syphilis.<sup>72</sup> In spite of a decline and re-emergence of syphilis, it does not appear to cycle and therefore there is a real possibility of eliminating syphilis.<sup>254</sup>

There are no effective vaccines against syphilis. Recent developments in the identification of *T. pallidum* immunogens may prove useful for vaccine development.<sup>51</sup>

Epidemiologic/presumptive treatment of all contacts of patients who were exposed within 90 days is essential. Public education about the sequelae and prevention of syphilis and other sexually transmitted diseases is paramount in the primary prevention of the disease.<sup>60</sup> Condom use reduces the transmission of syphilis and should be promoted in high-risk groups. Routine screening for syphilis is recommended in high risk groups, like STI clinic attendees, sex workers, intravenous drug users, and HIV positive persons, and this approach has been found effective in control of the disease. Mass screening is not recommended in areas with low prevalence, as it is not cost effective. Defining the efficacy of azithromycin for early syphilis might simplify therapy. Single dose, directly observed therapy with oral azithromycin, if found efficacious for incubating syphilis and useful in early syphilis may have a pivotal role to play in the control of syphilis, dealing with the crucial issue of patient compliance and the problems of delivering parenteral penicillin in non-clinical settings.<sup>72</sup>

## Targeted Mass Treatment

In several areas with high prevalence of syphilis, health workers have tried to reduce the spread of disease by treating everyone in the targeted group even if they do not exhibit the symptoms.<sup>255</sup> Between 1952 and 1969, under a WHO and UNICEF sponsored global campaign, health workers administered single dose of penicillin to 50 million people infected with yaws in 45 countries. This program almost eradicated yaws, which reappeared in 1990s. In some areas of Indonesia, health workers regularly treat sex workers with penicillin. In North America, a few smaller mass treatment interventions have been found useful in the control of syphilis.

In California, the incidence of syphilis declined by 27% among the migrant workers and by 51% among female sex workers after such an intervention in 1976–1977. Another intervention was reported to be successful in a cocaine-related syphilis outbreak.<sup>256</sup> However, in Greenland, during the late sixties, mass treatment with penicillin, and recently, in Canada, mass treatment with oral azithromycin did not show promising results.<sup>257</sup> The problems associated with mass treatment are high cost, side effects, drug resistance, and increased susceptibility to other infections. Currently, targeted mass treatment for syphilis is not recommended. If complete coverage of high-frequency transmitters cannot be achieved and if population mobility is relatively high, a rebound increase in the prevalence of syphilis can occur in the target population.<sup>258</sup>

### Summary

Infectious syphilis remains an important cause of morbidity and mortality worldwide, and primary and secondary syphilis significantly increase the risk of transmitting and acquiring HIV. Syphilis in pregnancy is a major cause of adverse pregnancy outcomes and perinatal morbidity and mortality. Although PCR tests are being increasingly used for the diagnosis of early syphilis, the cornerstone of diagnosis remains serological tests. Parenteral penicillin is the treatment of choice.

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# Late Syphilis

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## Introduction

Natural history studies have been used to describe two broad stages of syphilis—early and late. The early stage is characterized by occurrence of primary and secondary syphilitic manifestations. Rashes of secondary syphilis are known to recur up to 2 years after infection. After this period the disease enters a prolonged asymptomatic phase when the only sign of disease is positive serological tests. Most authorities consider 2 years as a cut off between early and late syphilis.

Late syphilis begins with a continuation of the early latent phase which is termed late latent syphilis. The Oslo study of untreated syphilis in the first half of the twentieth century was pivotal to our understanding of the natural history of syphilis, especially the outcome of late latent syphilis.<sup>1</sup> Without treatment, a third of the patients would have a spontaneous cure wherein the VDRL/RPR test becomes negative and there is no recurrence of disease. A further third of patients maintain a positive VDRL/RPR test but no sign of disease. The remaining third of patients would develop signs and symptoms of late syphilis: half with benign tertiary syphilis, a quarter with cardiovascular disease and a quarter with neurosyphilis. There is some overlap among these manifestations with some patients suffering from two or even three forms of late syphilis. It should also be noted that neurosyphilis can occur at any stage of syphilis, not just the late stage, and any patient with neurological signs and symptoms who has evidence of syphilis should be evaluated for neurosyphilis regardless of stage or HIV serostatus. For the sake of discussion, neurosyphilis will also be addressed in this chapter, but also may be considered elsewhere.

In the post antibiotic era, the incidence of most forms of late syphilis have shown a steady decline to such an extent that they have been relegated to isolated case reports. The advent of HIV infection since the 1980s has renewed interest in these manifestations. Several authors have suggested that HIV positive patients are more at risk of developing neurosyphilis.

Most studies on late syphilis, especially neurosyphilis, have been hampered with significant problems such as the inability

to culture the causative organism, difficulty in interpretation of serology and hence establishing the diagnosis, difficulty in defining a cure, inaccessibility of diagnostic material such as CSF, difficulty in distinguishing between re-infection and treatment failure, complex interaction with co-infection with HIV and paucity of cases. Hence current knowledge is based on mainly old studies in the pre-antibiotic and immediate post-antibiotic era.

## Epidemiology

As mentioned earlier, most forms of late syphilis have disappeared from clinical practice. Some forms of neurosyphilis are still seen today, especially in HIV infected patients.<sup>2</sup> Approximately one-third of patients with early syphilis have central nervous system invasion, however in HIV uninfected immunocompetent patients, it is generally subclinical and treatment with 2.4 MU benzathine penicillin eliminate it in overwhelming majority of patients.<sup>3</sup> It seems that in HIV infected patients, early invasion of central nervous system (CNS) may progress to early neurosyphilis due to failure of initial control. The reported high incidence of neurosyphilis in dually infected patients may also be related to high CSF abnormality due to opportunistic infections causing diagnostic confusion.<sup>4,5</sup>

All the major population statistical reports combine the figures for late latent syphilis with those of late syphilis. Hence it is difficult to ascertain the exact incidence of late syphilis in the 21st century.<sup>6,7</sup> In the United States, in 1976, the last year in which the Centers for Disease Control and Prevention recorded the number of neurosyphilis cases separately, there were 2903 cases of neurosyphilis of a total of 71,761 reported cases of syphilis.<sup>8</sup>

This chapter will address the various stages of late syphilis in the order of their appearance in the natural history.

## Late Latent Syphilis

This stage is the continuation of the early latent syphilis. The clinical relevance of distinguishing early and late latent stage is with respect of infectiousness (early latent syphilitic patients are considered to be more infectious than those in the late latent

stage due to paucity of *Treponemes* in the latter) and duration of treatment (more prolonged course of treatment needed in the late latent stage to account for the slowly dividing *Treponemes*).

Syphilis incognito<sup>9</sup> is a subtype of latent syphilis (early or late), which runs a subclinical course from the time of infection until its diagnosis by routine serologic screening. Patients with syphilis incognito do not give a history of earlier stages of syphilis and are diagnosed on routine screening with positive treponemal serology. It is unclear whether this is because of inadequate and inadvertent antibiotic use resulting in suppression of early syphilis manifestations, due to misdiagnosis of secondary syphilitic rashes or lack of awareness of painless primary chancres in inaccessible sites such as cervix or anal canal. Stratigos et al.<sup>9</sup> reported 67.5% of 528 patients with latent syphilis to have syphilis incognito in a series from Athens.

## DIAGNOSIS OF LATE LATENT SYPHILIS

By definition, patients are asymptomatic. Diagnosis is primarily by means of treponemal serology which includes positive non-specific serological tests, that is, VDRL/RPR, usually in low titers of 1 in 8 or less, and almost universally reactive specific treponemal tests, that is, TPPA/TPHA, MHA-TP and EIA tests. These tests are dealt in more detail in the chapter on infectious syphilis. Most guidelines advocate a thorough clinical examination and a chest X-ray to rule out systemic involvement. A negative VDRL/RPR test on peripheral blood suggests that neurosyphilis is unlikely<sup>10</sup> whereas a titer of 1:32 or more may predict CSF abnormalities.<sup>11</sup> A risk-benefit analysis of patients with late latent syphilis suggests that a lumbar puncture is unnecessary in these patients.<sup>12</sup> As debated in the section on asymptomatic neurosyphilis, various forms of penicillin are able to prevent progression of these cases to overt neurosyphilis.<sup>13</sup> Hence, a lumbar puncture is only recommended in late latent syphilis if there is treatment failure. Patients with HIV co-infection are dealt in a separate section.

## Neurosyphilis

Involvement of the CNS by *T. pallidum* is one of the most dreaded complication of syphilis and case reports in the post-antibiotic era of neurosyphilis remind physicians of the seriousness of this infection. As mentioned before the rates of neurosyphilis have steadily declined over the latter half of the twentieth century.

## CLASSIFICATION

Merritt and colleagues<sup>14</sup> (modified by Swartz et al.<sup>15</sup>) classified the various forms of neurosyphilis in the pre-antibiotic era but it is important to note that there is considerable overlap of these syndromes and many patients had features of different forms of neurosyphilis. (Table 37.1)

Neurosyphilis can also be divided into early and late forms.<sup>16</sup> Early neurosyphilis is commonly associated with CSF changes and involvement of cerebral blood vessels and meninges. It occurs within weeks to a few years after infection. It can be

**Table 37.1:** Classification of Neurosyphilis<sup>14,15</sup>

Type	Percent in whom predominantly seen
<b>Asymptomatic (early and late)</b>	31
<b>Meningeal</b>	20
Acute syphilitic meningitis	6
Meningovascular (including deafness)	11
Cerebral	Rare
Spinal	3
<b>Parenchymatous</b>	48
General paresis	12
Tabes dorsalis	30
Taboparesis (mixed)	3
Optic atrophy	3
<b>Gumma</b>	1
Cerebral	Rare
Spinal	Rare
Total	100

asymptomatic, may present as meningitis, with or without cranial nerve or eye involvement, as meningovascular disease or stroke. Late neurosyphilis mainly involves the meninges and brain or spinal cord parenchyma. This form is now extremely rare and occurs years to decades after primary infection. Manifestations of this stage include general paresis and tabes dorsalis.

## PATHOLOGY

There is evidence that *Treponemes* invade the CNS at a very early stage. CSF abnormalities were noted in 13% of patients with primary syphilis and 25–40% of patients with untreated secondary syphilis.<sup>17,18</sup> Without treatment, this invasion may resolve spontaneously, lead to asymptomatic syphilitic meningitis or develop into symptomatic acute syphilitic meningitis. The latter two conditions, if left untreated, may progress to meningovascular syphilis 5–12 years later, or tabes or paresis 18–25 years later. However, in many patients co-infected with HIV, neurosyphilis has been reported to occur at the early stage. This may be due to inability of the CNS to control the initial invasion by *Treponemes*.<sup>4</sup>

Acute syphilitic meningitis is associated with an inflammatory process involving the meninges and ependyma. A meningeal infiltrate of lymphocytes and plasma cells is seen around blood vessels. A prolonged inflammatory process results in fibroblastic organization leading to obstruction of CSF flow and hydrocephalus. Cranial nerves are affected due to compression by basilar exudates and fibrous organization. Third nerve involvement is commonly a result of raised intracranial pressure. Endarteritis of cerebral arteries associated with meningitis is responsible for the vascular association in the form of seizures and cerebral infarction/strokes.



Cerebrovascular syphilis shows the characteristic changes of endarteritis with perivascular infiltration with lymphocytes and plasma cells. Damage to the adventitia and media of medium to large-sized arteries, which leads to sub-intimal fibroblastic proliferation and subsequent luminal obliteration, results in cerebral infarction.

### EARLY ASYMPTOMATIC NEUROSYPHILIS

Abnormal CSF characterizes this stage and is difficult to diagnose as the patient is asymptomatic. Lumbar puncture is not advocated in early syphilis in the absence of symptoms and hence most patients with this condition will remain undiagnosed. However, the rarity of progression to overt neurosyphilis in the penicillin era indicates that treatment with antibiotics, whether intentional or not, results in complete resolution of these CSF abnormalities. The classic abnormalities described are 10–100 WBC/cm<sup>3</sup> which are predominantly lymphocytes, a protein of 50–100 mg/dl and a positive VDRL/RPR test in 50% of cases. The frequency of abnormal CSF findings increases until 12 to 18 months after initial infection following which there is a steady decline over many years with only 6.3% showing CSF changes at 20 years after infection in one report.<sup>19</sup> However, risk of symptomatic neurosyphilis increases in those patients with persistent CSF abnormalities. Patients with CSF changes at more than 5 years after infection developed neurologic disease in 87% of cases who had no treatment.<sup>20</sup>

Diagnostic significance of abnormal CSF findings in asymptomatic patients co-infected with HIV is unknown. CSF WBC may be elevated in these patients due to opportunistic infections or without any known cause; however, a CSF WBC greater than 20 appears to be a specific and sensitive criteria for the diagnosis of neurosyphilis in such a situation.<sup>21</sup> The risk of neurosyphilis is more in dually infected patients with CD4 count less than 350/μL and RPR titers of 1:32 or more.<sup>22</sup> Currently, CDC does not recommend CSF examination in early syphilis patients co-infected with HIV who have no CNS symptoms.<sup>23</sup>

### ACUTE SYPHILITIC MENINGITIS

According to a Merritt and Moore<sup>24</sup> report in the pre-antibiotic era, acute syphilitic meningitis is the first clinical manifestation of syphilis in a quarter of patients. The incubation period is less than 1 year and hence some patients may have a secondary syphilitic rash at the time of presentation. Symptoms of meningitis include acute or subacute onset of headache, nausea and vomiting associated with neck stiffness. It can present as cranial nerve palsies or with signs of increased intracranial pressure. Basilar meningitis commonly presents with asymmetric involvement of multiple cranial nerves, especially third, sixth, seventh, and eighth. Sensorineural deafness was seen in 20% of cases and may be preceded by tinnitus. The deafness is rapidly progressive with loss of higher frequencies. In isolated eighth nerve palsy, the CSF may be normal and there is no associated vestibular involvement.

Increased intracranial pressure resulting in acute syphilitic hydrocephalus was seen in a third of syphilitic meningitis cases in the pre-antibiotic era. This usually occurred in the first year of infection but has been reported up to 6 years after infection.

### Investigations

Both nonspecific and specific treponemal serological tests are positive in most patients. There is elevated CSF pressure on lumbar puncture and CSF shows mononuclear pleocytosis of 10–200 cells/cm<sup>3</sup>, raised CSF protein of up to 200 mg/dl, reduced glucose and elevated globulin level. The CSF VDRL/RPR is positive in a majority of cases.

### Differential Diagnosis

Lymphocytic meningitis can be caused by enteroviruses, *Leptospira*, *Borrelia* (Lyme disease), mycobacteria, or fungi. Use of imaging techniques in addition to specific serology and PCR tests would help to differentiate between these conditions.

### MENINGOVASCULAR SYPHILIS

This may affect the cerebrum or the spinal cord.

### CEREBROVASCULAR SYPHILIS

Infarction secondary to endarteritis is the primary pathology of cerebrovascular syphilis. It may affect any part of the CNS and invariably results from chronic meningitis described earlier. These manifestations commonly occur about 5–12 years after initial infection and affect the 30–50 year age group. It may be accompanied by symptoms of general paresis or tabes. Occasionally Argyll Robertson pupils may be present even in the absence of parenchymal involvement.

Focal neurological syndromes are the hallmark of this condition with most patients presenting with strokes (11.1%) and seizures (24.2%) as reported in a series of 241 patients from Virginia.<sup>25</sup> The most common artery involved is the middle cerebral artery but involvement of other arteries like anterior cerebral, posterior cerebral, basilar and posterior inferior cerebellar arteries is reported.<sup>15</sup> Although the syphilitic strokes are similar to arteriosclerotic thrombotic lesions, syphilitic thrombosis often affects the smaller branches resulting in less extensive infarcts. The onset is sudden in half the patients but in the other half may be preceded by symptoms of headache, dizziness, insomnia, and memory loss or mood disturbances over weeks or months. Personality and behavioral changes suggestive of general paresis may precede the stroke/seizures causing diagnostic confusion.

### Investigations

Treponemal serology is positive and CSF VDRL/RPR is positive in most cases. CSF examination shows pleocytosis with increased protein. “Beading” and diffuse irregularity of arteries on angiography, especially affecting anterior and middle cerebral

arteries is commonly seen.<sup>15,26</sup> The areas of arterial narrowing in syphilis are longer and smoother compared to that seen in arteriosclerosis. Neuroimaging confirm areas of ischemia or infarctions with low density areas on CT and hyperintense areas on T2 weighted MR scans.<sup>26</sup>

## Differential Diagnosis

Cerebrovascular accidents (CVA) in young adults should raise suspicion of cerebrovascular syphilis, especially normotensive patients with no other risk factor for thromboembolic disease. Diagnosis in older patients is difficult as they are at risk of other causes of CVA, such as atherosclerosis. History of untreated or partially treated syphilis, positive serological tests for syphilis and CSF examination helps in establishing the diagnosis.

Differential diagnosis includes causes of stroke, such as hypertension, atherosclerosis, cerebral thromboembolism, and various types of cerebral vasculitis.

## MENINGOVASCULAR SYPHILIS OF SPINAL CORD

Spinal syphilis was rare (3% in Merritt's series<sup>14</sup>) before the advent of penicillin and has become even rarer since. The spinal cord is affected in a similar manner as the brain, with extension of the meningeal inflammation leading to either parenchymal changes or vascular involvement or both. Syphilitic meningomyelitis is the most common form whilst, uncommonly, vascular thrombosis leads to acute syphilitic transverse myelitis.<sup>27</sup>

Syphilitic meningomyelitis presents 20–25 years after infection with a gradual onset weakness or paraesthesia of the legs, developing into paraparesis or asymmetric paraplegia.<sup>8</sup> Upper motor neurone involvement leads to classical signs of spastic paraparesis with hyper-reflexia, ankle clonus, absent abdominal reflexes and extensor plantar reflexes. Dorsal column involvement leads to loss of position and vibration sense in the lower limbs. The clinical picture may overlap with that of tabes or general paresis. Spinal vascular syphilis presents acutely similar to complete or incomplete transection of the spinal cord, usually at the thoracic level. Abrupt flaccid paraplegia, a clear sensory level on the trunk and urinary retention are classic findings. Prognosis is poor as there is little functional recovery with treatment.

## Investigations

Blood and CSF pictures are similar to that of cerebrovascular syphilis. Imaging would be useful but paucity of recent cases means there is very little literature on the subject.

## Differential Diagnosis

Multiple sclerosis and subacute combined degeneration should be excluded in patients with syphilitic meningomyelitis. Causes of acute transverse myelitis must be excluded in patients with acute onset flaccid paraplegia. Peripheral blood and CSF serology are useful to establish diagnosis.

## PARENCHYMATOUS NEUROSYPHILIS

General Paresis of the Insane (syn. Paretic neurosyphilis, dementia paralytica, general paresis).

Direct invasion of the cerebral parenchyma by Treponemes results in a meningo-encephalitis which is characterized by a clinical syndrome termed General Paresis of the Insane (GPI). It is a chronic progressive condition with an incubation period of 3–30 years. Males are more often affected than females.

Most patients present with gradual onset of symptoms while some patients may present acutely. Early symptoms are non-specific (irritability, fatigability, depression, impaired concentration, headaches, and insomnia) while more specific psychiatric symptoms appear later (impaired judgment and insight, depression or elation, confusion, disorientation, paranoia, and delusions). Most patients are diagnosed with depression initially<sup>28</sup> while 15–20% of patients may present with seizures.<sup>29</sup> Some patients present with memory loss, personality changes and impaired concentration in early stages. Delusions of grandeur occur only in 10–20% of cases.<sup>29</sup> Clinical signs include pupillary abnormalities, expressionless face, intention tremors, dysarthria and hyperactive reflexes. Argyll Robertson pupils are classically described in tabes dorsalis but are commonly seen with paresis as well. Pupils, which are initially large subsequently become small, unequal, and fixed with loss of pupillary reaction to light but preservation of the accommodation reaction.

The dementia is progressive (although uncommonly, some patients may show spontaneous short periods of improvement) resulting in death in a few months to a few years. Treatment in early stages is associated with a good prognosis however a communicating hydrocephalus is known to complicate recovery in some patients.<sup>30</sup>

## Investigations

CSF findings are typical of neurosyphilis with lymphocytic pleocytosis and raised proteins. Blood and CSF VDRL/RPR are usually positive however, in some cases negative non-treponemal CSF serology may cause diagnostic difficulty in late stages. FTA-ABS test on CSF may be falsely reactive due to diffusion of serum immunoglobulins into the CSF.<sup>31</sup> Analysis of intrathecal antibody synthesis using CSF-IgG index,<sup>32</sup> CSF:serum ratio of TPHA,<sup>31</sup> CSF IgM assay<sup>33</sup> and B cells in the CSF<sup>34</sup> have been proposed but not used commonly for diagnosis in clinical practice. A PCR test on CSF for *T. pallidum* has not been studied adequately in recent years. Brain imaging using computerized tomography may show signs of cerebral atrophy suggesting a demyelinating process with decreased attenuation of cerebral white matter (frontal and parietal lobes) and enlargement of cortical sulci and ventricular dilatation.<sup>35</sup> Gummas and areas of infarction may also be seen.

## Pathology

Meningeal thickening, cerebral atrophy (frontal and parietal lobes) with demyelination and granular ependymitis are characteristic changes seen in GPI.

## Differential Diagnosis

The clinical presentation along with characteristic CSF and radiological changes forms the basis of diagnosis. The diagnosis is more difficult in elderly patients with dementia with a positive treponemal serology and inconclusive CSF picture. Alzheimer disease, degenerative dementing disease and alcoholic brain disease are part of the differential diagnosis.

### TABES DORSALIS

This condition is a rarity in the post antibiotic era having accounted for a third of the neurosyphilis cases in the first half of the twentieth century. It occurs within 5–50 years after primary infection with a peak occurring at 10–20 years. Clinical picture constitutes a classic triad of symptoms (lightning pains, sensory ataxia, bladder disturbances) and signs (pupillary abnormalities, areflexia, positive Romberg sign). Lightning pains are described as sudden paroxysms of severe localized, transient stabbing or shooting pains in the legs or any other part of the body. Paraesthesia and hyperaesthesia in the areas affected by lightning pains are common. Visceral crises involving stomach (gastric crisis—epigastric pain, nausea, and vomiting), intestines (intestinal crisis—abdominal pain, and diarrhea), rectum (rectal crisis—tenesmus) and larynx (laryngeal crisis—hoarseness, stridor and pain in larynx) are rare manifestation of lightning pains. Involvement of the dorsal spinal columns leads to loss of vibration sense and proprioception in the lower limbs. Knee and ankle reflexes are reduced or lost whilst maintaining flexor plantar response. Sensory ataxia with a broad based stamping gait is a characteristic sign. Loss of deep pain perception results in Charcot joints (painless enlargement of knee joints due to repeated trauma, Figs. 37.1 and 37.2) and trophic ulcers on soles, especially at the base of the great toe. A third of the patients develop bladder disturbances and a tenth, rectal incontinence. Eye involvement is common with Argyll Robertson pupils (described earlier) in nearly half the patients. Optic atrophy and cranial nerve involvement (particularly, the second, third, and sixth nerve) leads to blindness, strabismus, ptosis and flabbiness of facial muscles giving a characteristic tabetic facies. Involvement of the eighth nerve may lead to deafness with or without associated vestibular abnormality.

The rate of progression of the disease may vary from 6 months to 25 years from onset to development of ataxia.<sup>31</sup> Eventually the disease process may burn out even without treatment.

### Investigations

In active disease, treponemal, and non-treponemal serology is positive on peripheral blood. CSF shows classic features of lymphocytic pleocytosis, elevated protein concentration and reactive non-treponemal serology. In the pre-antibiotic era, in patients with established clinical diagnosis, even in burnt out cases, non-treponemal tests on the CSF were rarely negative.



**Fig. 37.1.** Tabes dorsalis: Charcot knee joint; the left knee joint has large effusion and valgus deformity. *Courtesy: Dr. OP Arya: Sexually Transmitted Infections and AIDS in the Tropics.* Arya OP, Hart CA, eds. Wallingford, Oxon: CAB International, 1998: Fig. 7.1.5.



**Fig. 37.2:** Tabes dorsalis: X-ray of Charcot knee joint showing destructive changes, new bone formation and loose bodies. *Courtesy: Dr. RW Galloway: Sexually Transmitted Infections and AIDS in the Tropics.* Arya OP, Hart CA, eds. Wallingford, Oxon: CAB International, 1998: Fig. 7.1.6.

### Differential Diagnosis

Adie syndrome (absent deep tendon reflexes and myotonic pupils) can be differentiated on the basis of non-miotic pupils and absence of lightning pains and ataxia. Diabetic neuropathy may be associated with sluggish pupils, ptosis, areflexia, ataxia and burning neuropathic pain. Treponemal serology is able to distinguish this condition. Subacute combined degeneration of the spinal cord can mimic tabes with ataxia and bladder



disturbances, however, absence of lightning pains and extensor plantar reflexes help in the diagnosis.

### OPTIC ATROPHY

Optic atrophy may occur along with tabes or GPI or may be an isolated finding. Uveitis may also present as a presenting feature of neurosyphilis. Syphilitic optic atrophy presents with progressive visual loss in one eye followed by the same process in the other eye.

### GUMMA

Intracerebral gumma is very rare and presents as a space occupying lesion with raised intracranial pressure. CT scan shows a low-density non-enhancing lesion and angiography shows a hypervascular blush zone around the central focal area of necrosis.<sup>36</sup>

## Neurosyphilis in HIV Infection

Atypical presentation of neurosyphilis has been a subject of many case reports. In one series of HIV positive patients, prevalence of asymptomatic neurosyphilis of at least 1% was noted on the basis of positive CSF VDRL test.<sup>37</sup> However, there have been no large studies identifying an increase in symptomatic neurosyphilis. Large treatment studies of HIV-positive and HIV-negative patients have not found any significant differences in response to treatment.<sup>3</sup>

## Cardiovascular Syphilis

Involvement of the cardiovascular system classically manifests after 15–30 years of latency with a male to female ratio of 3:1 and there is some link with heavy manual work. Aortic aneurysm, aortic insufficiency, coronary artery stenosis and myocarditis are some of the manifestations of cardiovascular syphilis. The incidence of cardiovascular syphilis has gone down significantly since the advent of penicillin and only case reports can be found in today's literature.

### PATHOLOGY

Treponemes are presumed to possibly reach the aorta by way of lymphatics during the spirochaetemia occurring in the early stages of syphilis and lodge in the aortic wall. They remain there for many years before provoking inflammation, detected in the form of perivascular lymphocytes and plasma cells. Which factors trigger this inflammation in some patients and not in others is unclear. Endarteritis is the primary pathologic process in all forms of syphilis and this is especially true with cardiovascular involvement. The vasa vasorum supplying blood to the ascending and transverse aorta are especially susceptible to this process. Endarteritis of vasa vasorum leads to patchy necrosis of the aortic media resulting in focal scarring. Damage to the elastic tissue in the aortic wall leads to aortic dilatation and aneurysm formation. However, the other layers of the aortic wall are also affected. Fibrous thickening of the adventitial layer and thickening of the intima with atherosclerotic

changes are thought to be related to treponemal infection. Due to all these changes, the aortic wall shows the classical “tree barking” appearance on autopsy. Calcification of these plaques gives an egg-shell appearance on the chest X-ray.

Aortitis is the commonest lesion in cardiovascular syphilis; however, lesions involving the coronary ostia, aortic valves and myocardium have been described.<sup>38</sup> Myocarditis and gummatous involvement of the myocardium are rare. Granulomas in the myocardium result in fibrous scars and may cause complications in the form of ventricular arrhythmias and valvular dysfunction.

## Aortic Aneurysm

Syphilitic aneurysms were the most common manifestation of tertiary syphilis in the pre-antibiotic era.<sup>31</sup> The thoracic aorta was involved in the majority with over 60% affecting the ascending aorta and 25% involving the transverse arch.<sup>31</sup> These fusiform or saccular aneurysms rarely dissected because of the thickening of the aortic wall following chronic inflammation.<sup>38</sup> The clinical course is insidious with symptoms developing only when the aneurysm impinges on surrounding structures or if it erodes through the chest wall and presents as a mass on the chest wall. Persistent chest pain and secondary symptoms, such as hoarseness of voice due to recurrent laryngeal nerve involvement, are common presentations. Chest X-ray may show egg-shell calcification described earlier. However, similar changes are seen in atherosclerosis or in old age. Angiography is useful to delineate the exact extent of the aneurysm. Surgical resection is indicated in patients with expanding aneurysm and those with symptoms.

Associated aortic regurgitation due to stretching of the aortic valve occurred in about 30% patients with cardiovascular syphilis.<sup>31</sup> The degree of insufficiency was variable. Signs of aortic regurgitation included diastolic blowing murmur along the lower left sternal border, a tambour-like second heart sound and dilated hypertrophy of the left ventricle. Differential diagnosis includes infective endocarditis, congenital valvular malformation, Marfan syndrome, ankylosing spondylitis, Reiter syndrome, traumatic cusp dehiscence and aging. Management includes valve replacement for patients with symptoms and congestive cardiac failure. Ventricular hypertrophy may not resolve after surgery.

Syphilis can also affect the coronary arteries with involvement of the ostia and the proximal few millimeters of the coronary arteries. There is an obliterative endarteritis which may lead to ischemic heart disease and sudden death.

## Late Benign Syphilis

**Synonym:** Gumma

This is a proliferative destructive granuloma which may affect the skin, soft tissue or bony structures. Cutaneous gummas can cause significant disfigurement. Involvement of visceral organs and CNS present as space occupying lesions. In the post-antibiotic era, gummas have all but disappeared and only case reports are seen in modern literature.<sup>39,40</sup>

It is thought that the gumma is a hypersensitivity response to the presence of very few *Treponemes* in late stages of the infection. Gummas are nodules with central necrosis surrounded by inflammatory lymphocytic and mononuclear infiltrate. This granuloma is encapsulated by proliferating connective tissue. Multinucleate giant cells are rarely seen. The size varies from microscopic to several centimeters. On the skin, it forms an ulcer which heals with considerable scarring.

## SKIN

Nodular and nodulo-ulcerative lesion starts as a 1–5 mm in size brownish red, deep indurated nodule (Fig. 37.3). Multiple lesions occur in an arciform pattern and are mostly seen on the face, back, and extremities. These are indolent and may remain for weeks or months. Some lesions may break down and then heal leaving an atrophic non-contractile scar. New lesions may appear in the surrounding skin and extend in a serpiginous manner.<sup>31</sup> Solitary gumma is an extension of a granuloma in the subcutaneous layers and is commonly seen on the thighs, buttocks, shoulders, forehead, and scalp.<sup>31</sup> The necrotic material may discharge through a sinus onto the skin.

## BONES

Gumma of the bones were as common as those of the skin<sup>31</sup> in the pre antibiotic era. These present with localized pain, tenderness

and swelling. X-rays show periostitis, gummatous osteitis, and sclerosing osteitis.<sup>31</sup> Gummatous involvement of the nasal bones, hard palate, and nasal septum has been described.

## SOFT TISSUE

Gumma involving the tongue, stomach, liver, and myocardium lead to specific signs and symptoms relating to that particular organ.

## Treatment

### LATE SYPHILIS

The principles of antibiotic therapy in syphilis are described in the chapter on infectious syphilis.

### LATE LATENT SYPHILIS, CARDIOVASCULAR, AND LATE BENIGN SYPHILIS

Most guidelines now recommend three doses of Benzathine penicillin 2.4 million units at weekly intervals for these patients.<sup>23,41</sup> Alternative regimens include Procaine penicillin 600,000 units IM OD for 17 days, Doxycycline 200 mg BD for 28 days, Amoxycillin 2 g PO tds plus probenecid 500 mg PO qds for 28 days.<sup>41</sup> The response to treatment in these patients is difficult to assess. In asymptomatic patients the physician has to rely on the VDRL/RPR titer which is usually serofast at a low level. Failure of therapy is usually seen with an increase in these titers.

Cardiovascular and late benign syphilis are treated in the same manner as late latent syphilis due to lack of more specific data in the modern era.

### NEUROSYPHILIS

The introduction of penicillin in the 1940s improved the outcome of neurosyphilis. A large multicenter trial involving treatment of 1086 patients with GPI identified a total penicillin dose of 6 million units as adequate for therapy.<sup>42</sup> The Centers for Disease Control and Prevention 2010 guidelines recommend intravenous aqueous penicillin G 18–24 million units daily for 10–14 days or intramuscular procaine penicillin G 2.4 million units plus probenecid 500 mg PO qds for 10–14 days.<sup>23</sup> In the UK, the duration is for 17 days with the intramuscular route as the first option compared to the intravenous route. Alternative regimens include Doxycycline 200 mg BD for 28 days, Amoxycillin 2 g PO tds plus probenecid 500 mg PO qds for 28 days, or Ceftriaxone 2 g IM (with lidocaine as diluent) or IV (with water for injections as diluent) for 10–14 days. In patients allergic to Penicillin, Ceftriaxone may be used although there is a 10% risk of cross-reaction.

Post treatment CSF examination is essential to confirm cure until CSF changes are resolved. Failure of resolution of CSF changes at the end of 1 year should warrant retreatment. If relapse has not occurred for a period of 2 years then the patient is considered as cured.



**Fig. 37.3:** Painless, ulcerated gumma on shaft of the penis. Courtesy: Dr. RR Mittal, Patiala, India.

Most guidelines recommend the same regimens of therapy for HIV infected individuals as there was no difference in the outcomes in these patients in a large study although some experts believe that the response to treatment in terms of VDRL/RPR titers is sluggish in HIV positive patients.

### Summary

Lack of complete information on late syphilis is compounded by asymptomatic nature of the disease, lack of simple and definitive diagnostic criteria and few epidemiological studies because of the dwindling number of patients with late syphilis in the post antibiotic era. Asymptomatic neurosyphilis is common—does not require extra treatment but close observation on the serology and the patient is essential. However, awareness about the late phase of the disease is important because of its possible progression to ultimately involve CNS and CVS, and this makes it imperative to consider it in the differential diagnosis when the past history is suggestive of inadequate or irregular or non-penicillin treatment of syphilis. Associated HIV disease makes the interpretation of serology difficult and also hastens the involvement of CNS. Since neurosyphilis (symptomatic or asymptomatic) can occur at any stage of syphilis, not just late syphilis, it would be best considered as a specific entity. With this specific consideration of CNS involvement, other manifestations of late syphilis in the post-antibiotic era are relatively rare, but should be considered especially in HIV-infected individuals. Diagnosis may be challenging, but therapy with penicillin is still the preferred choice.

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## Introduction

Endemic treponematoses or tropical nonvenereal treponematoses include yaws, pinta, and endemic syphilis. The causative organisms belong to the order Spirochaetales, family of the Treponemataceae and genus *Treponema*. Yaws is caused by *T. pertenue*, pinta by *T. carateum*, and the causative organism of endemic syphilis is *T. endemicum*. The natural host for these organisms is man. At present, the causative agents of the different treponematoses cannot be distinguished from each other serologically, morphologically, or by other means.<sup>1</sup> The causative agents of nonvenereal and venereal treponematoses have shown minor genetic differences, but none of these variations can distinguish the subspecies.<sup>2</sup> They can be seen under the dark ground microscope as slender, silver threads coiled like a cork screw and have got a characteristic rapid spinning movement. The study of the pathology of the diseases caused by these bacteria is greatly hampered by the inability to culture any of these treponemes *in vitro*.<sup>3</sup> It has been postulated that treponematoses originated some 22,000 years ago in the Eurasian-African land mass. Poorest people of the world were affected and the diseases caused disfigurement, disability, and an economic burden.<sup>4</sup>

According to an estimate in 1996, the population at risk was about 34 million, i.e., 5% of the total world population (mainly infants, children and to a lesser extent, adolescents, and young adults). They all live in developing countries, with 21 million living in the so-called least developed countries. The regions which are affected the most are Africa and Southeast Asia, with some foci in central and South America, the Middle East, and Pacific Islands. The total number of cases estimated globally is 2.6 million and infectious cases number 460,000 of which 400,000 cases are in Africa. The number of disabled persons due to endemic treponematoses is estimated at 260,000 cases globally.<sup>5</sup>

The WHO department of control of neglected tropical diseases launched a global initiative in 2007 to eliminate yaws and other endemic treponematoses.

## HIV and Endemic Treponematoses

The immunodeficiency due to HIV might lead to reactivation of latent treponematoses. HIV-infected patients are more likely to carry a large number of treponemes and might disseminate these pathogenic treponemes more effectively than HIV-negative persons.<sup>6</sup>

## YAWS

Synonyms: Framboesia tropica (German, Dutch), pian (French), parangi, boubas (Portuguese), buba (Spanish), paru. Yaws is an ancient disease. It is a chronic, infectious, relapsing nonvenereal treponematosis.

The disease is seen in rural tropical areas where the humidity level is high and rainfall is heavy.<sup>2</sup> Other factors that favor transmission of yaws include poor socioeconomic conditions, lack of sanitation, overcrowding, and scanty clothing.<sup>7</sup> It is found in people who have little or no access to health services. Therefore, yaws is said to occur “at the end of the road”<sup>3</sup>.

## Etiology

It is caused by *T. pallidum* subspecies, *pertenue*. It is a regular, slender, spiral spirochete that is 8 µm in length and 0.2 µm in width. The number of coils vary from 8 to 16. It multiplies by transverse fission every 30 to 33 hours. *T. pertenue* is morphologically and serologically indistinguishable from *T. pallidum*, which causes venereal syphilis.<sup>8,9</sup> It does not cause congenital infections because it cannot cross the placenta. It is easily killed by drying and heat.

## Prevalence

Yaws is primarily a disease of children with a peak incidence between 6 and 10 years of age.<sup>10</sup> Some authors have described a sex difference,<sup>8</sup> i.e., it is more common in males than in females, but others feel that boys and girls are equally affected.<sup>11</sup>

It is mainly confined to the belt between the tropic of Capricorn and the tropic of Cancer. In Asia, it occurs in Indonesia, Papua

New Guinea, and the South Pacific. Cases, though in small numbers, are persistently reported from Sri Lanka and India. In India it was endemic in Andhra Pradesh, Madhya Pradesh, Maharashtra, Orissa, and Tamil Nadu prior to the mass treatment campaign in 1950.<sup>12</sup> In the Western Pacific region, three countries remain endemic—Papua New Guinea, the Solomon Islands, and Vanuata.<sup>13</sup> There are unconfirmed reports that Yaws is still present in some countries in sub-Saharan Africa and Western Pacific region. For example, in 2005 about 26,000 cases were reported in Ghana and about 18,000 cases were reported in Papua New Guinea.<sup>14</sup>

In 1952, a yaws control program was started in India with assistance from WHO and UNICEF. From 1952 to 1964, about 200,000 cases of Yaws were detected and treated in Andhra Pradesh, Madhya Pradesh, Maharashtra, and Orissa. The campaign reduced the incidence by 93%. Yaws re-emerged in 1977 in Madhya Pradesh.<sup>15</sup> A Yaws eradication program also took place in India in 1996–1997 in the Koraput district of Orissa. In 1996, 3571 cases were reported and by 2004 this had fallen to zero.

Yaws elimination is defined as Zero reporting of cases based on high-quality case searches validated by independent appraisals. Yaws eradication is defined as the absence of new cases for a continuous period of 3 years, supported by the absence of evidence of transmission through serosurveys among children aged <5 years, i.e., no seroreactivity to rapid plasma reagin or VDRL.

On September 16th 2006, yaws was eliminated from India and the government hopes to eradicate yaws by 2010.<sup>16</sup>

## Mode of Transmission

Yaws is transmitted nonvenereally by direct skin-to-skin contact. The infection spreads by close contact from an individual with an open lesion to an uninfected person with skin excoriations, scratches, bites, etc. The spirochetes cannot enter through the intact skin and breaks in continuity of the skin surface serve as portals.

Overcrowding and poor socioeconomic status favor transmission of the disease. The lack of water and soap for bathing and washing, and of shoes or clothing for children between the ages of 5 and 15 years are said to favor yaws transmission. There is no evidence to suggest indirect transmission by fomites or insects,<sup>17</sup> but theoretically it may be possible. Yaws is not transmitted sexually, but the presence of a genital lesion may cause confusion in making an accurate diagnosis.

## Clinical Features

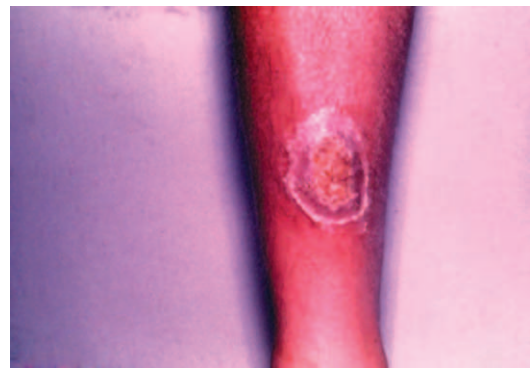
Yaws can be classified into the early infectious stage and the late noninfectious stage. Early yaws comprises primary and secondary stages, while late yaws, the tertiary stage. In the primary stage, skin lesions are seen at the site of inoculation and in the secondary stage widespread multiple skin lesions are seen due to dissemination of treponemes. The tertiary stage is characterized by deformities.

## Early Yaws

Incubation period is same as for syphilis, i.e., 9–90 days (average 3 weeks).<sup>18</sup> The organism gains entry through minor abrasions or lacerations and multiply at the site of infection, then invades the subcutaneous lymphatics and spreads through the blood stream. The skin lesions start as one or more nontender papules that later become crusted and ulcerated (Fig. 38.1). The initial lesion is called the “mother yaws” which can persist for up to 6 months and healing occurs spontaneously leaving a large atrophic and depressed scar.<sup>19</sup> Sometimes, friable ulcerated proliferative papillomatous lesions are seen, which are very rich in treponemes.

The initial lesion is followed by multiple, small, widespread, cutaneous papules—the daughter yaws (Figs. 38.2–38.4). Constitutional symptoms like fever, malaise, and generalized lymphadenopathy may be associated with these lesions. Other cutaneous lesions seen are macules, papules, maculopapules, micropapules, plaques, and nodules. Palms and soles may show hyperkeratosis (crab yaws) (Figs. 38.5 and 38.6). Lesions in the early stage of yaws usually disappear spontaneously, sometimes leaving behind a slight pigmentary change. Painful osteoperiostitis and dactylitis can occur.<sup>20</sup> Periungual lesions of the nail fold produce deformities called pianic-onychia and even shedding of the nail.

The early stage is followed by a variable period of latency, which can be detected by serological tests.



**Fig. 38.1:** Primary yaws on the lower leg. Necrotic center and a collarette of scales bordering the lesions. *Courtesy:* Dr. DS Nagreh, Penang, Malaysia.



**Fig. 38.2:** Crusted ulcerative lesion of early yaws on penis. *Courtesy:* Dr. DS Nagreh, Penang, Malaysia.





**Fig. 38.3:** Close-up of nodular lesions of secondary yaws—morphologically similar to primary lesion, except they are smaller and multiple. *Courtesy:* Dr. DS Nagreh, Penang, Malaysia.



**Fig. 38.4:** Peri-orificial 'verrucous' secondary yaws. *Courtesy:* Dr. DS Nagreh, Penang, Malaysia.



**Fig. 38.5:** Hyperkeratotic plaques of secondary yaws on soles. *Courtesy:* Dr. DS Nagreh, Penang, Malaysia.

### Late Yaws

Late stage develops in 10% of the patients after about 5 to 10 years.<sup>18</sup> It is characterized by destructive changes. Skin, soft tissue, cartilage, and the bone (Fig. 38.7) are the sites involved. Late manifestations include gangosa (destructive ulcerative rhinopharyngitis), gummata, juxta-articular nodes, contractures, and sabre tibia (Figs. 38.8 and 38.9). Gondou is a rare feature



**Fig. 38.6:** Hyperkeratotic plaques of secondary yaws on palms. *Courtesy:* Dr. DS Nagreh, Penang, Malaysia.



**Fig. 38.7:** Periostitis of the tibia in late yaws. *Courtesy:* Dr. Nagreh, Penang, Malaysia.

characterized by exostoses of nasal and adjacent bones. Neurologic and ophthalmologic abnormalities have been reported.<sup>21,22</sup> Roman and Roman in their review article argue that there is ample evidence for CNS, cardiovascular, and congenital infections in yaws.<sup>23</sup>

Vertical transmission, as is seen in venereal syphilis, does not occur in yaws.<sup>18,24</sup>

### Histopathology

Early lesions show acanthosis and papillomatosis. There is neutrophilic exocytosis, giving rise to intraepidermal microabscesses. The dermis is infiltrated mainly by plasma cells, but other cells like neutrophils, eosinophils, lymphocytes, and histiocytes may also be present. Blood vessels are affected usually



**Fig. 38.8:** Deformity of tibia in late yaws (Sabre tibia).  
*Courtesy: Dr. DS Nagreh, Penang, Malaysia.*



**Fig. 38.9:** Anterior bowing of tibia in late yaws. *Courtesy: Dr. DS Nagreh, Penang, Malaysia.*

only mildly in yaws, in contrast to syphilis.<sup>17</sup> A large number of treponemes can be demonstrated between epidermal cells by silver impregnation or immunofluorescence.

### Laboratory Findings

Treponemes can be demonstrated by dark ground examination from skin lesions in the early stage. The serological tests include venereal disease research laboratory (VDRL) test, *Treponema*

*pallidum* hemagglutination (TPHA), and fluorescent treponema antibody (FTA-Abs) test. The rapid plasma reagin (RPR) is a slide agglutination test to detect antibodies against yaws. The test is reliable, economical, reproducible, rapid, and easy to perform even under field conditions. The specificity and sensitivity of the test is similar to that of VDRL test.

### Diagnosis

The diagnosis of yaws is based on clinical features, supplemented by dark ground examination and serological tests. A typical presentation of yaws is in an individual who lives in an endemic area and presents with one or more of the following signs: ulcer with scab, papillomas, palmar/plantar hyperkeratosis.

### Differential Diagnosis

In the tropics, a variety of skin conditions should be differentiated from yaws, which include impetigo, ecthyma, tropical ulcers, Hansen's disease, chromoblastomycosis, cutaneous leishmaniasis, scabies, and viral infections like molluscum contagiosum.

### Treatment

Penicillin is the drug of choice. Resistance to penicillin has not yet been demonstrated.<sup>25</sup> A single injection of benzathine penicillin, in the dose of 600,000 units for children below 10 years and a dose of 1.2 million units for those aged over 10 years is recommended. Tetracycline and erythromycin have been advocated in patients who are sensitive to penicillin.<sup>17</sup>

Eradication of yaws is difficult,<sup>26</sup> because:

- (i) Untreated yaws is infectious for months or years after the onset of symptoms.
- (ii) Treponemes tend to persist in the CSF and lymph nodes after treatment.
- (iii) A vaccine is not available against yaws.
- (iv) Diagnosis may be difficult in nonendemic areas.

But with active case detection, treatment, surveillance, and community awareness, yaws is amenable to eradication.

### PINTA

Synonyms: Carate (in Colombia, Venezuela), mal del pinto (in Mexico), azul (in Chile, Peru), cute and morado. It is a chronic infectious disease caused by *T. carateum*. The organism is closely related to the causative agents of yaws, venereal, and endemic syphilis.<sup>18</sup>

The disease is endemic in tropical central and South America and is considered as a disease of western hemisphere.<sup>27</sup> Since the early seventies, pinta has been extinct from the world with the exception of few scattered areas in the Brazilian rain forest.<sup>28</sup> Imported cases from these regions have been reported from the eastern hemisphere also. There is a high incidence among people who live in primitive and unhygienic conditions. The

main reservoir of the disease is young adults, who have chronic skin lesions.<sup>27</sup> Transmission occurs by direct skin or mucous membrane contact. Fomites may play a role in the transmission of pinta, but it has not been proved conclusively.<sup>29</sup> The disease is predominantly seen in children and adolescents after the age of 10 to 15 years. Both sexes are equally affected.

## Clinical Features

Pinta can clinically manifest in two stages viz., early and late. Initial primary lesions and generalized cutaneous lesions are seen in the early stage. The late stage consists of the late latent and tertiary phase. The stages frequently overlap.

After an incubation period of 7 to 21 days, an initial papular lesion develops on the exposed parts of the body, usually the legs, the dorsum of the foot, the forearm, or the back of the hands. Sometimes, an erythematous scaly plaque may be seen. Local lymphadenopathy is common. The primary lesions heal spontaneously. After several months or even years, multiple, widespread, small lesions can appear which may be hypochromic, pigmented or erythematous. These secondary lesions are called "pintides".

The late stage develops after 2 to 5 years. It is characterized by achromia, disfiguring pigmentary changes, skin atrophy, and hyperkeratosis.<sup>1</sup> Pinta affects only the skin.<sup>18</sup> Systemic symptoms are not seen in pinta; the cardiovascular and central nervous systems are not involved. Pinta is a benign disease and the prognosis is good.

## Histopathology

The early lesion is characterized by acanthosis, exocytosis of lymphocytes, and loss of melanin and liquefaction degeneration in the basal layer. The dermis shows a mixed infiltrate of plasma cells, lymphocytes, histiocytes, and neutrophils. Melanophages are seen in the upper dermis.

## Differential Diagnosis

Skin disorders associated with changes in pigmentation should be considered in the differential diagnosis. These include vitiligo, pityriasis versicolor, pityriasis alba, tuberculoid leprosy, and erythema dyschromicum perstans.

## Diagnosis

Diagnosis is mainly clinical and can be confirmed by dark-ground microscopy and serology. Treponemes can be demonstrated with silver stains in all but long-standing depigmented lesions.<sup>30</sup>

## Treatment

Benzathine penicillin is the drug of choice. A single dose of 600,000 units in patients below 10 years and 1.2 million units in those aged over 10 years is used. In penicillin sensitive patients, either tetracycline or erythromycin may be used.

## ENDEMIC SYPHILIS

Synonyms: Bejel (Arabic), firjal, dichuchwa (Zimbabwe), loath. It is a chronic infectious, nonvenereal, endemic disease caused by *T. pallidum*, subspecies *endemicum*. The organism is closely related to *T. pallidum*. In dry hot climatic zones, endemic syphilis continues to cause a problem.<sup>31</sup>

Endemic syphilis is prevalent among people who live in crowded and unhygienic conditions. It is prevalent in the rural areas of Saudi Arabia, Saharan regions in Africa, and among Bedouin tribes in the Middle East. Endemic syphilis is seen in children between 2 and 15 years of age and also in adults from infected families.<sup>18</sup> Both sexes are equally affected. The disease is transmitted nonvenereally by direct skin to skin or mouth to mouth contact. Transmission of the disease by insects has been suspected by some but has not been proven. The lesions may occur in and around the mouth as the result of using the same drinking vessels. The breastfed child can acquire this disease from a chancre on the nipple of infected mother. The spread of endemic syphilis can be controlled by improving living conditions.<sup>32</sup>

## Clinical Features

### Primary Stage

The lesions are seen in the oropharyngeal mucosa<sup>18</sup> and usually go unnoticed by patients, as they are small and transient.<sup>33</sup>

### Secondary Stage

The clinical features resemble that of secondary syphilis and are characterized by asymptomatic skin lesions, mucous patches, and lymphadenopathy. Other features are the development of condylomata lata and osteoperiostitis. The skin lesions are characterized by multiple, shallow, painless ulcers involving lips, buccal mucosa, tongue, or tonsils. Patients may also develop treponemal laryngitis leading to hoarseness of voice.

### Late Stage

This stage is characterized by the involvement of skin, bones, and cartilage. There can be destruction of the nose and palate. Clinically, patients present with gumma of the nasopharynx, larynx, skin, and bone. These lesions may progress to ulcers, which heal with depigmentation or scars with peripheral hyperpigmentation. Most frequently associated ocular findings are uveitis, choroiditis, chorioretinitis, and optic atrophy.<sup>34</sup> Neurologic and cardiovascular involvement is rare. The exact reason is not known. The causative agent, although antigenically related to *T. pallidum*, could be a mutant or a different spirochete that cannot invade the cardiovascular or nervous systems.<sup>34</sup>

## ATTENUATED ENDEMIC SYPHILIS

A clinically attenuated form of endemic syphilis has been described by Pace et al. in Saudi Arabia. In this form, the number, severity, and duration of both early and late lesions are reduced,



and the majority of seropositive persons have latent disease. The most common manifestation is persistent pain in the legs, often associated with radiological evidence of osteoperiostitis of the tibia and fibula.<sup>35</sup>

## Histopathology

The microscopic findings resemble that of venereal syphilis. There is a perivascular infiltration of plasma cells and lymphocytes. In the early stages, treponemes can be demonstrated by silver stains.

## Differential Diagnosis

Endemic syphilis must be differentiated from venereal syphilis, yaws, and pinta. The diagnosis is based on the clinical features, history, and country of origin. Other cutaneous conditions to be differentiated are psoriasis, pityriasis rosea, and lichen planus.

## Treatment

The drug of choice is benzathine penicillin and the dosage schedule is the same as described for the other treponematoses.

### Summary

- The conditions included under endemic treponematoses are yaws, pinta, and endemic syphilis.
- Yaws is caused by *T. pertenue* and is clinically characterized by crusted ulcerative lesion in the early stage and by destructive changes in the late stage.
- Pinta is a chronic infectious disease caused by *T. carateum* and clinically manifests in two stages viz. early and late.
- Endemic syphilis is caused by the subspecies of *T. pallidum*, and it is clinically characterized by three stages viz primary, secondary, and late stage.
- Benzathine penicillin is the drug of choice in endemic treponematoses.

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## Introduction

Gonorrhea, caused by the obligate human pathogen *Neisseria gonorrhoeae* (the gonococcus), is the second most prevalent bacterial sexually transmitted disease (STD) globally. Gonorrhea, including its severe complications, has remained a major public health concern worldwide and causes substantial morbidity and economical cost, especially calculated as disability-adjusted life years.<sup>1,2</sup> In 2005, according to the World Health Organization (WHO) estimates there were 88 million new cases among adults worldwide. The incidences have remained high in many less-resourced settings, and also since mid- or late-1990s shown increasing trends even in many developed and more industrialized countries. Most worryingly, the bacterium has now developed resistance to nearly all antimicrobials introduced for treatment of gonorrhea, and it is a fear that gonorrhea may become untreatable in certain circumstances and especially in some settings.<sup>3–5</sup>

*N. gonorrhoeae* colonizes and infects primarily the mucosa of urogenital, anorectal, pharyngeal, and ocular regions. The clinical spectrum of gonococcal infection extends from asymptomatic mucosal colonization to frank inflammatory mucosal disease (urethritis, cervicitis, pharyngitis, proctitis, conjunctivitis). If untreated, or inappropriately treated, the urogenital infection may ascend to the upper genital tract and cause local complications such as salpingitis, pelvic inflammatory disease (PID), and epididymitis, and even serious systemic complications such as disseminated gonococcal infection (DGI), arthritis, dermatitis, endocarditis, and meningitis. Apart from causing disastrous sequelae such as ectopic pregnancy, infertility, and blindness (due to ophthalmia neonatorum), gonorrhea significantly facilitates HIV transmission through increased viral shedding from the inflamed mucosa.<sup>6</sup>

## History

Gonorrhea is one of the oldest diseases known to mankind. References suggestive of this infection were found in ancient Egyptian, Roman, Greek, Chinese, Japanese, Vedic, and Biblical (Book of Leviticus) citations. Hippocrates (ca. 460–370 BC) described the condition of “strangury” (presumably acute

gonorrhea), as a result of excessive indulgence in the pleasures of Venus. The Roman physician Celsus was aware of gonorrhea and catheterized patients with urethral stricture. Galen (ca. 130–200 AD) coined the term “gonorrhea” (gono=seed; rrhoea=flow) under the impression that the male discharge was an involuntary loss of semen (spermatorrhea). In an ancient Indian medical treatise, “dysuria” was dealt exhaustively in the chapter “Diseases of the urinary passages” by Sushruta (ca. 500 AD).<sup>7–9</sup>

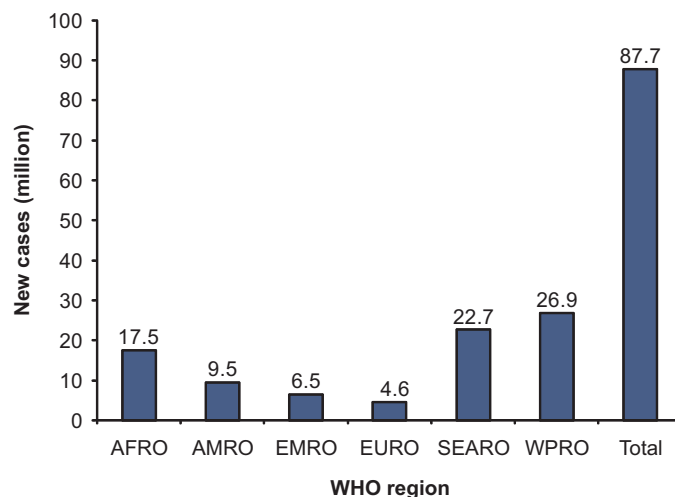
Guillaume de Salicet (13th Century AD) may have been the first to describe the venereal nature by attributing the disease to the impurities retained under the male prepuce after contact with an unclean female. The term “clap” for gonorrhea first appeared in print in 1378. While the sexual transmission and contagious nature of this infection were being established in the early 15th century, controversy arose in western Europe regarding the etiology of syphilis and gonorrhea. In 1530, Paracelsus taught his disciples that gonorrhea was an early feature of syphilis. This view further gained support from the classic experiment of John Hunter who, in 1767, developed syphilis after self-inoculation of pus from the penile urethra of a patient infected with gonorrhea (who was co-infected with syphilis, but this was unknown at the time). This concept persisted for a long period despite the fact that Benjamin Bell in 1792 contended that both these diseases are separate entities. Later, Phillippe Ricord finally clarified and established the distinctive nature of both these diseases in 1831.<sup>7–9</sup>

However, full understanding was first achieved when the etiologic agent of gonorrhea, initially named “Micrococcus der Gonorrhoe,” was identified in 1879 by Albert Neisser in the stained smears of purulent urethral, vaginal, and conjunctival exudates.<sup>10</sup> Leistikow and Loeffler in 1882 grew the organism *in vitro* on culture media of blood serum and gelatin.<sup>11</sup> Bumm further established the causal relationship between the organism and the disease by producing the characteristic signs and symptoms after inoculating the male urethra with the growth obtained from culture. Demonstration of the bacteria as Gram-negative diplococci was possible with Gram staining introduced by Hans Gram in 1884.<sup>12</sup> Thayer and Blummer documented gonococcal

endocarditis and septicemia before the end of 19th century. The carbohydrate utilization test for distinguishing *Neisseria* species and oxidase test were introduced by Elser and Huntoon in 1909,<sup>13</sup> and Gordon and McLeod in 1928,<sup>14</sup> respectively. In 1964, the selective Thayer–Martin medium,<sup>15</sup> greatly facilitated the diagnosis of gonorrhea, especially in women. This was followed by many new microbiological revelations, such as the demonstration of variations in the virulence of gonococci with different colonial morphology by Kellogg and co-workers in 1963,<sup>16</sup> and elucidation of ultrastructural and immunological features of *N. gonorrhoeae*. Non-culture-based diagnostic methods were then developed during the subsequent decades. These included serological assays, such as complement fixation test, for detection of gonococcal antibodies, and antigen detection methods like direct immunofluorescence using fluorescent antibody techniques and enzyme-linked immunosorbent assays.<sup>17–21</sup> During the last two decades, genetic methods for diagnosis, such as nucleic acid hybridization (NAH) tests and nucleic acid amplification tests (NAATs), have been rapidly replacing the culture diagnostics in many developed, industrialized countries.<sup>17–26</sup> Therapy for gonorrhea has undergone several changes, replacing the old horrible therapies, such as urethral astringents, soundings, and mechanical devices with chemical therapy initially with urethral irrigation with potassium permanganate solution and silver nitrate, and later in 1936 the first antimicrobial agents, the sulfonamides,<sup>7,9,27,28</sup> followed by penicillin in 1943<sup>29</sup> were introduced for treatment. For further information on antimicrobial treatment of gonorrhea (vide infra).

## Epidemiology of Gonorrhea

Gonorrhea is the second most prevalent bacterial STD globally and has remained a major public health concern worldwide. In 1999, 62 million new cases of gonorrhea were estimated among adults (15–49 years of age) globally by the WHO.<sup>30</sup> Forty-four (71%) million of these cases were in South and South-East Asia, and Sub-Saharan Africa. In developing or less-resourced settings, the estimated number of new cases (in million) were 12.12 for males (15.09 for females) in South and South-East Asia, 8.19 for males (8.84 for females) in Sub-Saharan Africa, and 3.26 for males (4.01 for females) in Latin America and the Caribbean. In more developed industrialized settings, the number of cases were substantially lower, for instance 0.49 for males (0.63 for females) in western Europe, 0.72 for males (0.84 for females) in North America, and 1.59 for males (1.68 for females) in East Asia and the Pacific. In 2005, 88 million new cases among adults worldwide were estimated by the WHO, the WHO South-East Asia region (23 million cases) and the WHO Western Pacific region (27 million cases) accounted for 57% of the global burden of new infections (Fig. 39.1) (WHO. *Prevalence and Incidence In 2005 Of Sexually Transmitted Infections: Methods And Results*. Geneva: World Health Organization 2011. In Press). The incidences have remained high in many developing less-resourced settings, and also since mid- or late-1990s shown



**Fig. 39.1:** Estimated new cases (million) of gonorrhea by WHO region among adults between the ages of 15 and 49 years, 2005. *Source:* WHO. *Prevalence and incidence in 2005 of sexually transmitted infections: methods and results*. Geneva. World Health Organization, 2011. In Press.

increasing trends, after approximately two to three decades of decline, in many developed, more industrialized countries such as in several Western European countries. Furthermore, due to the sub-optimal diagnostics, and incomplete case reporting and epidemiological surveillance in many countries, the reported incidences are also underestimated in many countries worldwide. The mentioned decline in gonorrhea rates during the 1970s and 1980s in, for example, many Western European countries and in the USA was probably due to multifaceted reasons, widespread education resulting in safer and more protected sexual behavior, improved diagnostic methods, appropriate antibiotic treatment, more effective contact tracing and, information about and fear of HIV and acquired immunodeficiency syndrome (AIDS) from the mid-1980s and onward.

The risk factors for gonorrhea widely differ in divergent societies but may include poverty, unemployment, migration of populations, illiteracy, early onset of sexual activity, being unmarried, being man who have sex with man (MSM), previous gonorrhea or other STD, concomitant other STD, young age, many new or multiple partners, inconsistent condom use, drug use and commercial sex.

## Biology of *Neisseria gonorrhoeae*

*N. gonorrhoeae* belongs to the family Neisseriaceae that includes five genera, i.e., *Neisseria*, *Kingella*, *Eikenella*, *Simonsiella*, and *Alysiella*.<sup>17</sup> The genus *Neisseria* contains two human pathogenic species, *N. gonorrhoeae* and *N. meningitidis*, and approximately 30 apathogenic commensal species that inhabit, e.g., the mouth and upper respiratory tract, but also rarely can be found in the urogenital tract. *N. gonorrhoeae* is a Gram-negative, aerobic, capnophilic, non-flagellated, non-sporulating, and oxidase and catalase producing coccus. In microscopy, *N. gonorrhoeae* (1.25–



1.6 × 0.7–0.8 μm in size) is typically observed in pairs (diplococci) with adjacent sides concave, i.e., appears in a characteristic kidney or coffee bean morphology. *N. gonorrhoeae* is fastidious and requires complex nutritionally enriched culture medium for *in vitro* growth. The bacterium can only utilize glucose, lactate or pyruvate as carbon source that is used in the species-verifying carbohydrate utilization test in which *N. gonorrhoeae* only degrades glucose (not maltose, fructose, sucrose or lactose). Human is the only natural host for *N. gonorrhoeae*, which survives poorly outside the human body due to its sensitivity to extreme temperatures, desiccation, oxidation and toxic substances. Ideal *in vitro* growth is obtained at 35–37°C in a 4–6% CO<sub>2</sub> atmosphere at a pH of about 6.5–7.5.<sup>9,17,18,20,26</sup>

Different *N. gonorrhoeae* strains display a high heterogeneity, genetically and phenotypically. This is due to its extensive genetic exchange within the species and with related species, using transformation (natural competence during entire life cycle) and conjugation (plasmid DNA), that results in recombination of partial or complete genes, high mutational frequency, and many phase-variable genes. In fact, *N. gonorrhoeae* has a non-clonal, sexual, and panmictic population structure. This high variability of *N. gonorrhoeae* is valuable for evasion or adaptation to the immune response of the host and for development and spread of antibiotic resistance mechanisms. These properties make the bacteria effective in persisting without severely damaging the host, i.e., in producing mildly symptomatic or asymptomatic infection.<sup>26</sup>

## Molecular Structures of *N. gonorrhoeae*

### GENOME OF *N. GONORRHOEA*

#### Chromosome

Already in 2000, the first genome of a gonococcal strain (FA1090) was assembled as one contig (2,153,922 base pairs (bp); GenBank accession no. AE004969). Recently, additional 16 genomes were finished and published online (n=14; [http://www.broadinstitute.org/annotation/genome/neisseria\\_gonorrhoeae/GenomeDescriptions.html](http://www.broadinstitute.org/annotation/genome/neisseria_gonorrhoeae/GenomeDescriptions.html)) or in scientific papers (n=2).<sup>31,32</sup> All these genomes had a size of 2.1–2.2 Mb, 52–53% GC content, and encoded 2100–2300 genes.

#### Plasmids

**Cryptic plasmid:** In 1973, a cryptic plasmid in *N. gonorrhoeae* was first reported. The plasmid is present in the majority of strains, but not in all auxotypes of *N. gonorrhoeae*.<sup>33</sup>

**β-lactamase encoding plasmids:** In 1976, two different β-lactamase producing plasmids in *N. gonorrhoeae* strains from South-East Asia and Sub-Saharan West Africa were reported from the USA and the United Kingdom, respectively.<sup>34,35</sup> The origin of these plasmids might be a *Haemophilus* species. The β-lactamase (penicillinase) was of TEM-1 type, which causes high-level penicillin resistance by hydrolyzing the cyclic amide

bond in the β-lactam ring. Penicillinase producing *N. gonorrhoeae* (PPNG) strains and these “Asian” and “African” plasmids are now globally widespread.<sup>5,26</sup> However, other types of β-lactamase encoding plasmids have also been described, e.g., the Rio/Toronto, Nimes, New Zealand, and recently Johannesburg plasmid. The Asian plasmid is probably the ancestral plasmid from which all these plasmids have been derived by means of insertions and/or deletions (indels).<sup>36,37</sup>

**Conjugative plasmids:** The first *N. gonorrhoeae* conjugative plasmid was identified in 1974.<sup>33</sup> This plasmid can transfer β-lactamase encoding plasmids between *N. gonorrhoeae* strains, and also to other bacteria like *N. meningitidis*. A derivative of the conjugative plasmid, a *tet*(M)-carrying conjugative plasmid, was described in 1985.<sup>38</sup> This plasmid was assigned the American *tet*(M) plasmid, expressed the TetM determinant initially identified in *Streptococcus*, and mediated high-level resistance to tetracycline. In 1991, the homologous Dutch *tet*(M) plasmid was described,<sup>39</sup> and a Uruguayan *tet*(M) plasmid has also been proposed.<sup>40</sup> Nowadays, tetracycline-resistant *N. gonorrhoeae* (TRNG) with the *tet*(M)-carrying self-mobilizing plasmids are widespread.<sup>5,26</sup>

### Outer Membrane Structures of *N. gonorrhoeae*

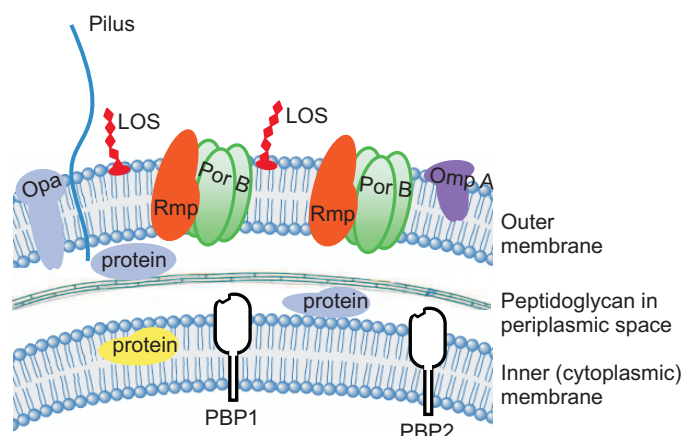
Outer membrane structures of *N. gonorrhoeae*, e.g., pilus, lipooligosaccharides (LOS), PorB, and Opa proteins are involved in the adhesion to the epithelial surface of the human host, invasion through the epithelial cell layer, and interactions with leukocytes. These structures have been extensively studied to elucidate the pathogenicity of gonorrhea, virulence of different strains, targets for diagnostics or potential vaccine candidates, and for phenotypic and genotypic characterization of *N. gonorrhoeae*.<sup>26</sup>

### Cell Wall and Outer Membrane

The cell wall consists of a Gram-negative bilayered outer membrane (phospholipids, LOS, and proteins) overlying a relatively thin peptidoglycan layer (in the periplasm) containing N-acetyl glucosamine, N-acetyl muramic acid, glutamic acid, diaminopimelic acid, and alanine. The bilayered inner membrane (cytoplasmic membrane) envelops the colloidal system of cytoplasm composed of organic and inorganic solutes dispersed in a viscous solution.<sup>9,20</sup> A schematic drawing of the cell wall is seen in Fig. 39.2.

### Lipooligosaccharide

The LOS consists of a lipid A moiety, which confines the endotoxic activity eliciting a host immune response, and a core oligosaccharide (composed of keto-deoxyoctanoic (KDO) acid and glucose, heptose, galactose, glucosamine, and/or galactosamine). The LOS is involved in adhesion, invasion, and toxicity of host epithelial cells. LOS is a target for bactericidal and chemotactic antibodies, however, sialylation of the LOS increases the antigenic variation and affects the invasion of epithelial cells, inhibits bactericidal activities of antibodies against PorB, LOS,



**Fig. 39.2:** Schematic drawing of the cell wall in *Neisseria gonorrhoeae* showing molecular structures such as pilus, lipooligosaccharide (LOS), opacity (Opa) protein, reduction modifiable protein (Rmp), the porin PorB, the outer membrane protein A (OmpA), penicillin binding protein 1 (PBP1) and PBP2. For example, the MtrCDE efflux pump and the IgA1 proteases, which are described in the text, are not shown. The figure was initially prepared by Dr. Susanne Jacobsson (Örebro University Hospital, Sweden) and then modified by the author (Unemo M).

and Opa proteins, phagocytosis of neutrophils, and complement activation by factor H binding, and may consequently result in serum resistance.<sup>9,41–43</sup> Intrastrain as well as interstrain variations of the antigenicity, lengths, and/or presence of any of the three oligosaccharide side chains, the number of LOS components expressed, and/or the relative concentration of the various components are frequent.<sup>9,41–43</sup>

## Pili

Pili are hair-like appendages, composed of thousands of pilin (PilE) protein sub-units in association with some other pilus-associated proteins that are extending several micrometers outside the bacterial cell. Pili are associated with the initial adhesion to human epithelial cells, they promote virulence by preventing neutrophilic phagocytosis, and mature pili or at least the major subunit of the pilus fibre, PilE, and PilC are essential for a high-level transformation of exogenous DNA.<sup>9,44</sup> High-frequency antigenic variation of pili results predominantly from recombinational events between several variable chromosomal silent *pilS* loci, in which the genes lack the 5'-end and promoter region of a functional PilE encoding gene, and usually one expressed *pilE* locus, encoding PilE. Hypervariable sequences of *pilS* may also be subject to horizontal exchange between the different *pilS* genes and to interstrain recombination.<sup>9,45</sup> Phase variation by on/off switch in the expression of PilC, a pilus-associated protein that is involved in biogenesis and adherence functions of the pilus, is also frequent.<sup>9,44,45</sup>

## Porin Protein

PorB (previously named major or principal outer membrane protein (MOMP/POMP), Protein I (P.I), or Por) is universally

present in the outer membrane, physically proximate to the LOS and reduction modifiable protein (Rmp), as trimeric pore-forming transmembrane proteins (porins) that allow small hydrophilic solutes and anions to diffuse through the outer membrane.<sup>9,46,47</sup> PorB is a target for bactericidal opsonic antibodies, however, it also comprises the ability to translocate into the cell membrane of eukaryotic cells, induces apoptosis of target cells, is involved in Opa-mediated and also Opa-independent invasion of epithelial cells, mediates evasion of complement-dependent bactericidal activities, and interferes with the activation, degranulation, and phagocytosis of neutrophils.<sup>9,46–50</sup> Any individual gonococcal strain expresses only one of two different groups of the proteins PorB1a and PorB1b.

## Opacity Protein

The outer membrane opacity (Opa) proteins, previously named heat-modifiable proteins or Protein II (P.II), contribute to colony opacity when cultured on specific media.<sup>51</sup> The Opa proteins facilitate intimate attachment between gonococci within culture colonies, and attachment to and invasion of epithelial cells and neutrophils of the host.<sup>9,51–54</sup> Up to 12 genetic loci encoding the Opa proteins exist in each strain, which may express none, one or several (usually 4–5) of these 12 antigenically different proteins.<sup>9,51–53</sup> Antigenic variation occurs because of variable expression of the different *Opa* genes.<sup>9,52,54</sup> Intragenic recombinations also occur in the *Opa* genes within and between lineages, and mutations further increase the heterogeneity of the *Opa* genes, and result in a higher level of antigenic variation and evasion of the host immune system.<sup>9,52,54</sup>

## Other Proteins

Rmp (previously named P.III) is a conserved and immunogenic protein, which is closely associated with the PorB porin in the outer membrane. Rmp is constitutively expressed, and non-bactericidal antibodies that recognize this protein, or homologous proteins in other *Neisseria* species, may block the bactericidal complement-dependent activity of antibodies that recognize, e.g., PorB and LOS.<sup>9,20,55</sup> Immunoglobulin A1 (IgA1) proteases, which are extracellularly secreted by pathogenic *Neisseria*, have been proposed to promote mucosal colonization due to their degradation of IgA1 antibodies. However, more recent studies have suggested that the IgA1 proteases are not a significant factor in the pathogenesis in the lower urogenital tract of the female.<sup>56</sup> Nevertheless, the IgA1 proteases may be important for intracellular survival in epithelial cells through alterations of the lysosomes.<sup>57</sup>

## Characterization of *N. gonorrhoeae* for Epidemiological Purposes

The epidemiologic characteristics of gonorrhea and of the heterogeneous *N. gonorrhoeae* strains fluctuate over time in both local and global perspectives. Thus, discriminative, reproducible,

and precise characterization of the bacteria can result in increased knowledge about strain populations in the community, about temporal and geographic changes, as well as concerning the emergence and transmission of certain (e.g., those that are more virulent or antibiotic resistant) strains. This information can be very valuable, together with epidemiological information, for identifying core groups and risk behaviors, test-of-cure and contact tracing, recommending effective antimicrobial treatment, and for the development of improved control measures and targeted interventions.<sup>58</sup>

## PHENOTYPIC CHARACTERIZATION

### Auxotyping

The first method for characterization of *N. gonorrhoeae*, auxotyping, was described in 1973.<sup>59,60</sup> Auxotyping divides strains into auxotypes based on their divergent nutritional requirements for amino acids, purines, pyrimidines, and vitamins. This method was earlier helpful in assessing the potential virulence, invasiveness,<sup>61–63</sup> antimicrobial susceptibility, and genetic constitution of various gonococcal strains.

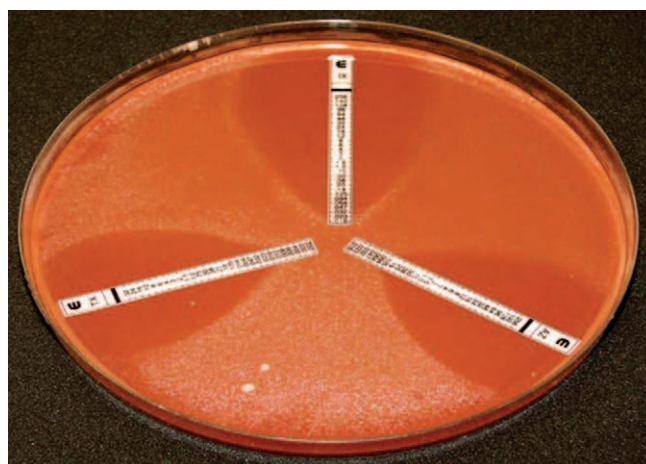
### PorB-based Serological Characterization

Serogroup (WI [PorB1a protein] or WII/III [PorB1b protein]) determination and the sub-dividing serovar determination, e.g., by using co-agglutination technique, with monoclonal antibodies (MAbs) are based on antigenic diversities of the outer membrane protein PorB. This has been the most widely used approach for serological characterization of *N. gonorrhoeae* and during recent decades mainly internationally more widely used Genetic Systems panel,<sup>64</sup> and the Pharmacia panel<sup>65</sup> of MAbs have been used.

### Antimicrobial Susceptibility Testing

Historically, the antibiograms of *N. gonorrhoeae* strains were used to determine relationships between bacterial isolates. However, the antibiograms comprise a low discriminatory ability between isolates and are not stable over time. Antibiograms should not be used as a reliable epidemiological characterization method. Nevertheless, antibiograms may supplement other characterization methods. The antibiograms also generate valuable clinical information and are essential for monitoring of the changing patterns of antibiotic susceptibility, thereby contributing to early warnings of emergence of resistance to different antibiotics.<sup>58</sup>

Agar dilution method is the gold standard method for susceptibility testing or determination of the minimum inhibitory concentration (MIC) of different antimicrobials. However, this method can be labor intensive and less suited for routine susceptibility testing, especially if a low number of strains are tested, and therefore a standardized and quality assured Etest method is commonly used (Fig. 39.3). Some disk diffusion methods are also in use, however, these require pronounced standardization and appropriate quality controls to attain a high level of reproducibility and reflection of the true MIC of



**Fig. 39.3:** Antimicrobial susceptibility testing of *Neisseria gonorrhoeae* using the Etest method.

the different antimicrobials.  $\beta$ -lactamase production is often analyzed by a chromogenic cephalosporin test, using nitrocefin disks or solution.<sup>26</sup>

Unfortunately, the phenotypic epidemiological characterization methods suffer from several disadvantages, e.g., sub-optimal discriminatory ability, limited access to MAbs of adequate quality and directed against all newly evolved antigenic epitopes, problems concerning reproducibility, and subjectiveness.<sup>58</sup> All conclusions regarding strain type and distribution acquired using phenotypic characterization methods should be interpreted with caution.<sup>58</sup>

## GENOTYPIC CHARACTERIZATION

Over the past two decades, to overcome the limitations of the phenotypic characterization methods many more powerful molecular (mostly DNA-based) characterization methods have been developed. These methods can be broadly divided into two groups—those methods involving analysis of DNA banding patterns by gel electrophoresis (gel-based DNA-based typing method) and those based on DNA sequence analysis (DNA sequence-based typing methods). Gel-based DNA-based typing methods include plasmid content analysis or restriction fragment length polymorphism (RFLP) determination using pulsed-field gel electrophoresis (PFGE), ribotyping, and Opa-typing. DNA sequence-based typing methods include full- or extended-length *porB* sequence analysis, *N. gonorrhoeae* multi-antigen sequence typing (NG-MAST), and multi-locus sequence typing (MLST). A recent review in detail describe all these methods, their usefulness, and provides recommendations when each method could be beneficially used.<sup>58</sup>

In general, appropriate, validated, and quality assured genotypic methods based on DNA sequencing have been internationally recommended for use, if available and affordable, and the selection of the appropriate genotypic method should be guided by its performance characteristics and whether short-term epidemiology (microepidemiology) or long-term and/or global epidemiology (macroepidemiology) matters are being investigated. Accordingly,



the questions asked in relation to the specific situation should guide the use of the most effective typing method or methods and, the typing results should be interpreted with the actual scientific, clinical, epidemiologic, or other information. Currently, for microepidemiological questions, the best methods for fast, objective, portable, highly discriminatory, reproducible, typeable, and high-throughput characterization are NG-MAST (examines the variable internal fragments of *porB* and *tbpB*), or full- or extended-length *porB* gene sequencing. However, PFGE (potentially indexing the whole genome) and Opa typing (examines the 12 Opa genes) can be valuable in specific situations, i.e., extreme microepidemiology, despite their limitations. For macroepidemiological studies and phylogenetic studies, DNA sequencing of chromosomal housekeeping genes, such as MLST, can provide a more nuanced understanding; however, the choice of appropriate and informative housekeeping genes are imperative.<sup>58</sup>

## Pathogenesis of Gonorrhea

*N. gonorrhoeae* has a predilection for non-ciliated columnar and cuboidal epithelium in adults. After the bacterium enters into the urogenital tract of the host, it adheres to the mucosal cells initially by means of pili, and then the outer membrane proteins, in particular, Opa proteins, but also iC3b, LOS, OmpA, and PorB facilitate an intimate adhesion and subsequent internalization and transcytosis. Simultaneously with the attachment, gonococcal LOS (endotoxin) also inhibits ciliary motility and damages proximate ciliated cells.

Following adherence, the organism is enfolded by pseudopods and pinocytosed by the epithelial cells where it divides and multiplies. Intracellularly, the organisms are resistant to immune attack. Gonococcal invasion is mediated also by the outer membrane PorB protein. After adherence, the PorB protein is translocated from the bacterial cell membrane to the epithelial cell membrane. The PorB1a protein is more effectively transferred into the epithelial membranes compared to PorB1b. Epithelial cell damage is mediated by release of certain enzymes like phospholipase and peptidase or due to LOS and peptidoglycan (both comprising endotoxic activity).<sup>9,20</sup>

The organisms are then exocytosed into the sub-mucosal region where they elicit a severe neutrophilic response and form microabscesses followed by exudation of purulent material into the lumen of the infected organ. The LOS antigens elicit the C5a-dependent chemotactic response.<sup>9,20,66</sup>

When the attack is prolonged, there is proliferation of the epithelium with subsequent formation of a stratified epithelial layer. Ultimately, keratinization and fibrosis occur leading to scarring and stricture formation. The infiltrate at this stage consists of lymphocytes and plasma cells besides polymorphonuclear leukocytes (PMNL) and eosinophils.<sup>9</sup>

## Disease Transmission

*N. gonorrhoeae* is an obligate pathogen and infected human is the only natural reservoir of the bacterium. *N. gonorrhoeae*

is primarily transmitted by direct human-to-human contact between the mucosal membranes of the urogenital tract, anal canal, or the oropharynx, mainly during sexual activities (vaginal or anal intercourse, or oral sex [fellatio or cunnilingus]). The efficiency of transmission of gonorrhea depends on anatomic sites infected, anatomic site exposed, and the number of exposures. The transmission efficiency (transmission through one exposure [vaginal intercourse]) has been estimated to be 20% from an infected woman to an uninfected man; however, following four exposures the transmission efficiency increases to 60–80%. The transmission efficiency from an infected man to an uninfected woman has been estimated to be as high as 50–90%.<sup>67,68</sup> In a study from 2000, the probable source of anorectal gonorrhea in MSM was determined; urethra and pharynx were the site of infection in 72% and 20%, respectively, of the cases.<sup>69</sup> A prospective cohort study examining brothel-based female commercial sex workers who practiced oral sex revealed that 5.2% of the sex workers contracted pharyngeal gonorrhea.<sup>70</sup> Transmission of the disease from pharynx to urethra can occur.<sup>71</sup> Neonates can be infected during passage through the birth canal if the mother has urogenital gonorrhea. This non-sexual transmission mainly causes ocular infections in the neonates (ophthalmia neonatorum).

Transmission by fomites or through non-sexual routes is extremely rare and there is no convincing evidence that any transmission occurs by toilet seats or droplet infection.

Gonorrhea is initiated as a pyogenic infection of the urethra in males and the endocervix in females. The incubation period varies from 1 to 14 days, with an average of 2–7 days. However, urogenital gonorrhea is asymptomatic in approximately 50–80% of women and 2–10% of men (varies by population studied, diagnostic methods used, duration of infection, etc.).<sup>9,21,72,73</sup> Anorectal and oropharyngeal gonorrhea, which can be common among MSM but also increasing in prevalence in heterosexual individuals in several countries, are very frequently asymptomatic. All these asymptomatic individuals form a reservoir of infection, which can effectively be further transmitted as well as progress into severe complications and sequelae.

## Clinical Manifestations of Symptomatic Gonorrhea

The clinical spectrum of gonococcal infection are listed in Table 39.1.

### ACUTE UROGENITAL GONORRHEA IN MEN

This clinical manifestation mainly presents as *acute anterior urethritis*, which is characterized by symptoms of dysuria and voluminous urethral discharge. The patient can have a profuse, yellow to yellowish-green purulent discharge, edematous lips of the external urinary meatus and associated perimeatal erythema (Fig. 39.4). Tender inguinal lymphadenopathy may be present. About one-quarter of the patients develop only a scant or minimally purulent exudate indistinguishable from non-gonococcal urethritis and a minority may never develop

**Table 39.1:** Clinical Spectrum of Gonococcal Infection

Asymptomatic infections	
<ul style="list-style-type: none"> <li>• Urethra</li> <li>• Endocervix</li> <li>• Rectum</li> <li>• Pharynx</li> </ul>	
Symptomatic infections	
<ul style="list-style-type: none"> <li>• Urethritis</li> <li>• Cervicitis</li> <li>• Bartholinitis</li> <li>• Balanoposthitis</li> <li>• Proctitis</li> <li>• Pharyngitis</li> <li>• Conjunctivitis</li> <li>• Vulvovaginitis</li> </ul>	
Local complications	
Male	Female
<ul style="list-style-type: none"> <li>• Epididymitis</li> <li>• Lymphangitis</li> <li>• Penile edema</li> <li>• Periurethral abscess</li> <li>• Prostatitis</li> <li>• Phimosis, Paraphimosis</li> <li>• Tysonitis, Littritis, Cowperitis</li> <li>• Seminal vesiculitis</li> <li>• Trigonitis</li> <li>• Watering-can perineum</li> <li>• Sterility</li> </ul>	<ul style="list-style-type: none"> <li>• Bartholin abscess</li> <li>• PID—salpingitis, pelvic abscess, pyosalpinx</li> <li>• Lymphangitis</li> <li>• Skeinitis</li> <li>• Parametritis</li> <li>• Cystitis</li> <li>• Infertility</li> </ul>
Systemic complications	
DGI—arthritis, dermatitis, tenosynovitis, endocarditis, myocarditis, pericarditis, meningitis, pneumonitis, hepatitis, pyelonephritis, Fitz Hugh–Curtis syndrome, septicemia (gonococcemia)	

\*PID: Pelvic Inflammatory Disease; DGI: Disseminated Gonococcal Infection



**Fig. 39.4:** Acute gonococcal urethritis (male) showing purulent urethral discharge. *Courtesy:* Dr. David Lewis, Johannesburg, South Africa.

overt signs and symptoms of urethritis. If appropriate treatment is not initiated, *posterior urethritis* may ensue in approximately 10–14 days, which presents as frequency of micturition, urgency, occasional strangury, and rarely tenesmus. Erection may be painful. In severe cases, few drops of blood at the end of micturition may be noticed.<sup>21</sup>

Acute gonococcal infection may involve the glands of Tyson, periurethral glands of Littre and paraurethral glands. *Acute tysonitis* presents as a pea-sized uni- or bilateral, erythematous, and tender swelling on either side of the frenulum. It may rupture spontaneously discharging pus which contains gonococci. *Periurethral gland involvement* presents as small follicular abscesses in the urethral wall. These coalesce to form a large abscess that infiltrates the corpus spongiosum leading to painful erection or ventral angulation of the penis. It may rupture to form a discharging sinus on the penile skin. The majority of these abscesses are localized along the bulbar part of the urethra and fossa navicularis. *Inflammation of the paraurethral glands* is observed as erythema, edema, and pus discharge from the paraurethral ducts present on either side of the external meatus. *Gonococcal balanitis* may rarely occur in uncircumcised patients. Pustular lesions over the penile skin associated with shallow ulceration around the frenulum may also develop.

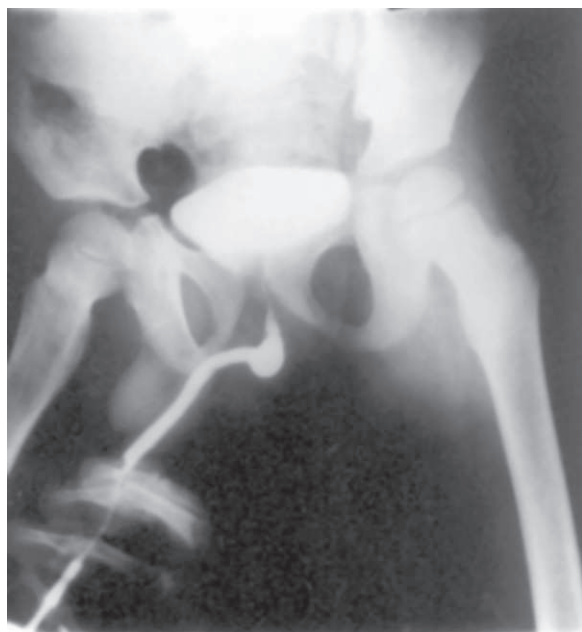
Acute cowperitis, prostatitis, seminal vesiculitis, and epididymitis are additional acute complications in males especially when the posterior urethra is affected. In *acute cowperitis*, the patient experiences pain and heaviness in the perineum. It may be associated with increased frequency of micturition or pain on defecation. Acute retention of urine due to reactive spasm of the posterior urethra may occur. Abscess formation can occur which is palpated on per rectum examination as a unilateral, tender mass between the layers of the triangular ligament in the perineum. In *acute prostatitis*, there is suprapubic discomfort, pain on defecation or even retention of urine. Rectal examination reveals an enlarged, edematous tender and fluctuant prostate. Formation of a prostatic abscess is heralded by high-grade fever associated with constitutional features, increased frequency or acute retention of urine, pain on defecation or tenesmus, and terminal dysuria. It is palpable as a large, tender, and tense swelling bulging into the rectum. It may rupture into the urethra resulting in profuse urethral discharge, or into the rectum causing acute proctitis. It may also lead to sinus formation in the perineum or adjoining skin. *Seminal vesiculitis* is associated with painful penile erection and ejaculation, or occasionally blood-stained semen. On per rectal examination, inflamed seminal vesicles can be palpated as elongated, swollen, sausage-shaped masses. *Gonococcal epididymitis* is rare. Infection occurs either by lymphatic spread or as a result of retrograde passage of urine along the lumen of the vas deferens to the epididymis secondary to excessive pressure during urethrovesicular irrigation, vigorous prostatic massage, urethral instrumentation, or excessive sexual indulgence. The condition is usually unilateral and the lower pole of the epididymis is initially affected. At the onset, symptoms of urethritis often cease temporarily and on examination the epididymis is swollen,

infiltrated, and exquisitely tender in association with redness and swelling of the overlying skin. Hydrocele formation may occur.<sup>21</sup>

### COMPLICATED UROGENITAL GONORRHEA IN MEN

Even in absence of appropriate treatment, spontaneous resolution occurs in the majority of urogenital cases within 4–6 weeks, with 95% of cases becoming asymptomatic within approximately 6 months. In rare instances, if the patient goes untreated or is inappropriately treated, serious sequelae may ensue. The patient may develop urethral strictures (Fig. 39.5), fistulae leading to “watering-can perineum” (Fig. 39.6), chronic littritis, cowperitis, prostatitis, seminal vesiculitis or epididymitis. Penile lymphangitis associated with regional lymphadenitis and penile edema (bull-headed clap) are other complications.

*Urethral strictures* may be annular involving a localized area of the urethra or “diaphragmatic” affecting a larger segment. The bulb of the urethra is the most frequently affected region, although any part may be involved. The urethral mucosa appears pale and firm in the area of the stricture. It can be detected on urethroscopy or by urethrogram. *Chronic littritis* presents as small firm nodules in the urethral wall. In *chronic cowperitis*, the patient complains of pain or heaviness in the perineum. An organized, tender abscess can be palpated pointing towards the perineum. *Chronic prostatitis* is recognized as continued symptoms as observed for acute over long time period. *Seminal vesiculitis* is characterized by “morning gleet” or frequent nocturnal emissions. Per rectal examination reveals a fusiform, indurated swelling on either side of the prostate. *Chronic epididymitis* presents as a fibrous nodule or nodular thickening, palpable at the root of scrotum.



**Fig. 39.5:** Urethrogram showing urethral stricture in male patient with complicated gonorrhea.



**Fig. 39.6:** “Watering-can perineum”-complicated gonorrhea (male) with streaks of urine from fistulae during micturition.

Sub-acute exacerbations may occur giving rise to pain, swelling, and tenderness. Recurrent episodes lead to blockade of the lumen resulting in stricture formation and sterility.

### ACUTE UROGENITAL GONORRHEA IN WOMEN

Uncomplicated gonorrhea in women remains asymptomatic in more than 50% of the cases and, accordingly, these women may act as an important reservoir of infection. These patients are diagnosed on the basis of screening or because their sexual partners are diagnosed with gonorrhea (contact tracing). The primary site of infection in females is the endocervical canal. The bacterium initially colonizes the lower urogenital tract such as the urethra, Bartholin and Skene glands and ascends to involve the cervix, and possibly subsequently the upper genital tract, i.e., the uterus, fallopian tubes, and the pelvis, whereas the vulva, vagina, and bladder are relatively spared. If symptomatic, acute gonococcal infection in females most frequently presents as *endocervicitis*, which is characterized by purulent vaginal discharge, dysuria, and sometimes post-coital bleeding. On speculum examination, copious pus emanating from the external cervical os can be visualized. There is severe erythema and edema of the cervix, and associated mucosal bleeding induced by swabbing the endocervix. Cervical erosions may also be present. Urethral discharge often goes unnoticed in females. Purulent discharge may be expressed by massaging the urethra from above downwards through the anterior vaginal wall. Endocervicitis may result in blockade of the cervical glands and formation of retention cysts or Nabothian follicles that protrude into the vaginal portion of cervix.<sup>21,74</sup>

*Acute skenitis* presents as tenderness in the terminal part of urethra and a bead of pus can be expressed at the ductal orifice (Fig. 39.7). It may commonly lead to abscess formation, which is felt as a tender, indurated mass on either side of the terminal urethra. In *acute bartholinitis*, the patient complains of pain and difficulty on walking and heaviness of the genitalia. Bartholin





**Fig. 39.7:** Skene gland abscess opening in distal urethra.

abscess is palpable as a tender, fluctuant mass at the junction of the upper two-thirds and lower third of the labia majora. A bead of pus can be expressed from the ductal opening on the inner surface of labia minora at the junction of lower and middle third. Acute *gonococcal vulvitis* is rare and may present as edema, erythema, and tenderness of the labia. Pus emanating from between the labia minora causes intertrigo and excoriation of the groins and thighs. *Gonococcal cystitis* and *trigonitis* may be occurring but are extremely rare.

### COMPLICATED UROGENITAL GONORRHEA IN WOMEN

PID is the most common local complication, which according to early studies can occur in 10–20% of untreated cases with acute urogenital gonorrhea.<sup>75</sup> The incidence of gonococcal PID is highest during the early proliferative phase of the menstrual cycle. This is at least partly due to changes in both the function of complement system and antibacterial activity of serum secondary to changes in sex hormone levels.<sup>76</sup> Symptomatic PID is less prevalent among women who use oral contraceptives.<sup>77</sup> Acute salpingitis usually occurs by retrograde intraluminal spread of infection along the surface of the endometrium. There is exudation of pus into the lumen of fallopian tubes with associated inflammation which can cause blockade of the fimbriated ends, resulting in pyosalpinx. The tubes may become adherent to the ovary, the central area of which breaks down to form a tubo-ovarian abscess. The infection can spread to the pouch of Douglas or pelvic peritoneum resulting in pelvic abscess or peritonitis. Acute salpingitis presents as acute lower abdominal pain accompanied by fever and constitutional features, menstrual irregularities or dyspareunia.<sup>21,75–77</sup>

On examination, localized tenderness in the iliac fossae associated with lower abdominal rigidity and guarding can be elicited. Bimanual pelvic examination reveals pain in the lateral fornices and on moving the cervix. A tender, fluctuant mass suggestive of pyosalpinx or tuboovarian abscess can also be palpated through the lateral fornices. Pelvic abscess presents as a tender, boggy mass in the pouch of Douglas and pus containing gonococci can be obtained by culdocentesis. Pelvic peritonitis is diagnosed by the presence of constitutional features with lower abdominal

rigidity and rebound tenderness. It is usually associated with fever and constitutional symptoms, raised erythrocyte sedimentation rate (ESR), leukocytosis, and elevated levels of C-reactive protein. PID is a serious health problem resulting in an increased risk of tubal infertility, ectopic pregnancy or chronic pelvic pain.<sup>21,75–78</sup>

Organization of pus in the pelvic peritoneum leads to adhesions between pelvic organs and the intestines, referred to as frozen pelvis. Fibrous bands can constrict the intestines causing intestinal obstruction. These bands pull the cervix to one side and the uterus may be bound down in a retroverted position.

Chronic urethritis, skenitis, bartholinitis, and proctitis are other possible complications in women.

### ANORECTAL GONORRHEA

Gonococcal proctitis in males usually results from anal coitus in passive MSM.<sup>79</sup> However, it may also be acquired via the oropharynx following orogenital sexual contact.<sup>80</sup> In women, the rectal mucosa is infected in up to 35–50% of cases with gonococcal cervicitis consequent upon perineal contamination with infected cervical secretions. According to studies in the 1980s, it is the only site of infection in 5% of women with gonorrhea.<sup>21,81,82</sup> However, changed sexual behavior, including more frequent anal intercourse also among heterosexual individuals, during the recent decades may have increased this figure, especially in some settings.

The signs and symptoms vary from minimal anal pruritus, painless mucopurulent discharge, and scant rectal bleeding to severe rectal pain and tenesmus associated with blood and mucus in the stool. Proctoscopy reveals red, edematous, and friable rectal mucosa that bleeds easily. Pus is usually evident on the mucosal surface and erosions may be present. Perianal and ischiorectal abscesses or anal fissures may develop.<sup>21</sup>

### PHARYNGEAL GONORRHEA

Oropharyngeal infection has been reported in about 3–7% of heterosexual men with gonorrhea, 10–25% of infected MSM and 10–20% of infected women.<sup>21,79,81</sup> However, also for this manifestation changed sexual behavior, including more frequent oral sex, during the last decades may have increased these figures, especially in some settings. Oropharynx is the sole site of infection in approximately 5% of cases. The infection is transmitted by orogenital contact and is more efficiently acquired by fellatio than by cunnilingus.<sup>80</sup> The symptoms are usually absent or mild in 90% of cases, although in a few instances, acute pharyngitis or tonsillitis may occur associated with fever and cervical lymphadenopathy. Pharyngeal gonorrhea may be a risk factor for developing DGI.<sup>81</sup>

### GONOCOCCAL CONJUNCTIVITIS

Gonococcal conjunctivitis is a rare entity in adults and most commonly seen in patients with concomitant urogenital and anorectal gonorrhea as a consequence of direct contamination by fingers or towels. The condition may vary from asymptomatic or mild infection to severe forms resulting in corneal ulceration and panophthalmitis.<sup>82</sup>

## DISSEMINATED GONOCOCCAL INFECTION

DGI results from hematogenous spread of infection to sites remote from the focus of infection. Sialylation of the LOS results in resistance to the bactericidal action of serum, an attribute necessary for dissemination into the blood to occur. DGI is also referred to as the 'acute arthritis-dermatitis syndrome'. The incidence of DGI has been shown in studies from the 1970s and 1980s to vary from 0.2% to 3% in patients with untreated mucosal gonorrhea,<sup>83–86</sup> however, these figures also vary, temporally and geographically, due to the gonococcal strain population circulating in different settings. This is because some gonococcal strains (which vary in prevalence, temporally and geographically), such as the AHU- auxotypes, have been shown to be more virulent and/or invasive, and accordingly more strongly associated with DGI.<sup>61,63</sup> Although the hematogenous spread of infection from a primary focus is implicated in the pathogenesis of DGI, the inability to detect viable organisms in blood, synovial fluid or skin in a significant number of patients suggests that additional factors may be important. An immune mechanism has been postulated since immune complexes have been detected in culture-negative skin lesions and the synovium. Occasional occurrence of immune-mediated skin lesions such as erythema nodosum and erythema multiforme might further support this hypothesis.<sup>87</sup> Based on culture characteristics, patients with clinical manifestations of DGI are classified into proven, probable, and possible cases. Individuals with positive cultures from blood, joint fluid or skin lesions are considered to have proven DGI and constitute less than 50% of cases. Patients with negative cultures from distant sites but with proven infection of the urogenital tract, anorectal tract or the pharynx are considered probable DGI cases and constitute the majority of cases. Individuals presenting with the characteristic findings of DGI but with negative cultures are referred to as having possible DGI.<sup>21,85</sup>

The characteristic clinical findings include suppurative arthritis and skin lesions. Overt arthritis occurs in 30–40% of patients with DGI.<sup>84,85</sup> It is a purulent asymmetric polyarthritis with onset in the 3–4 weeks of infection and affecting females more commonly than males. Wrist, ankle, knee, and the metacarpophalangeal joints are commonly involved. The patient develops high-grade fever, severe joint pain with swelling, erythema, and limitation of movement. It leads to destruction of the articular surfaces, narrowing of the joint space and ankylosis. Aspiration of the synovial joint fluid usually reveals leukocyte count of 30,000–80,000 PMNL/mm<sup>3</sup> (average 40,000 PMNL/mm<sup>3</sup>) and gonococci may be demonstrated on microscopy and culture. Around 60% of patients present without a detectable synovial effusion and over 90% of these have an associated skin rash or tenosynovitis.<sup>88</sup>

Gonococcal dermatitis is usually the presenting feature of DGI. The rash reported in 59–77% of DGI cases presents as tender, necrotic pustules with irregular hemorrhagic border and erythematous base, involving the distal aspect of the limbs overlying the small joints, palms, and soles but sparing the scalp,

face, and mouth. The number of lesions ranges from about 5 to 20. Other morphological variants include macules, papules, pustules, bullae, petechiae or ecchymoses. These lesions are seen in the various stages of development and resolve in 3–4 days with residual brownish discoloration. The rash is associated with high-grade fever, arthralgia, and tenosynovitis. Gonococci can be occasionally demonstrated in cultures from skin lesions and more frequently by immunofluorescent staining methods.<sup>89</sup>

DGI is considered more common in females, and male to female ratio of 1:4 has been reported.<sup>90</sup> Gonococcal septicemia occurs 7–30 days after primary infection and commonly within 7 days following menstruation. The primary mucosal infection in DGI is usually asymptomatic with a low chance of developing concurrent epididymitis or PID. This may be the result of impaired PMNL chemotaxis and reduced complement system activation. This leads to less mucosal inflammation and a greater opportunity for hematogenous spread.<sup>90</sup> Pregnancy and the perimenstrual period are two other risk factors for DGI. This is at least partly due to associated changes in gonococcal phenotype from opaque (Opa expressing) to transparent (mainly Opa-; which is more resistant to the killing action of normal serum) in conjunction with alterations in vaginal pH, cervical mucus, and genital flora.<sup>84</sup> Pharyngeal gonorrhea is also associated with increased risk of DGI. The role of immunosuppression secondary to alcoholism, steroids, intravenous (IV) drug use or systemic lupus erythematosus is unclear but these may contribute to a small number of cases particularly those with recurrent episodes of DGI. Individuals with complement deficiency, especially of factors C7–C9, either inherited or acquired, are predisposed to DGI, since complement activation plays a central role in controlling the spread of *N. gonorrhoeae* by acting as a chemoattractant for PMNL, opsonizing bacteria, and via the antibody–complement-mediated bactericidal activity of serum.<sup>21,86</sup> Most of the DGI cases have been caused by strains of the AHU-auxotype,<sup>61,63</sup> that is also associated with asymptomatic urethral infection in men,<sup>62,85</sup> susceptibility to penicillin,<sup>61,63</sup> and resistance to complement-dependent bactericidal action of normal human serum.<sup>9,21,61,63</sup> Furthermore, PorB1a isolates have been associated with invasive disease like DGI, and this may be affected by the fact that PorB1a but not PorB1b also promotes Opa-independent invasion of epithelial cells, as well as possibly that they inhibit the complement system and chemotactic response.<sup>21,62,91</sup>

Hematological investigations reveal leukocytosis usually not exceeding 20,000/mm<sup>3</sup>, a raised ESR (>50 mm), anemia, and elevated transaminases. Gonococci are detected on blood culture in one-third of the cases and synovial fluid cultures are positive in half the patients with a purulent effusion. Cervical cultures are positive in 90% of women, urethral cultures in 50% of men, pharyngeal cultures in 20% cases, rectal cultures in 15% of cases, and skin cultures in approximately 5% of the patients.<sup>21,88</sup>

Complications of DGI include myocarditis, endocarditis, pericarditis, meningitis, anterior uveitis, hepatitis, and perihepatitis. Endocarditis occurs in approximately 1–3% of the patients with

DGI.<sup>85</sup> Death may occur as a result of aortic valve incompetence and congestive cardiac failure.<sup>89</sup>

## GONORRHEA IN PREGNANCY

Gonococcal infection may have a devastating impact on both the pregnant woman and the outcome of pregnancy. Prior to 7–12 weeks of gestation, there is a relatively high risk of developing salpingitis and PID. After this period, the chances of developing PID are less, mainly due to local cervical factors that are modified under the influence of progesterone. Cervical mucus becomes thick and impermeable to the gonococci and the high progesterone concentration inhibits the growth of *N. gonorrhoeae*. After the 12th week of gestation, the chorion gets attached to the endometrial decidua, thus obliterating the intrauterine cavity and preventing ascending infection. Under such circumstances, gonococcal chorioamnionitis may occur which leads to septic abortion. It also increases the risk of premature rupture of membranes, preterm births, prematurity, perinatal mortality, or low birth weight.<sup>92</sup> Following child-birth, approximately 47% of women with intrapartum gonorrhea have been shown to develop postpartum endometritis, salpingitis, and puerperal sepsis.<sup>93</sup>

The prevalence of pharyngeal gonorrhea is also higher in pregnant women. In approximately 15–35% of pregnant women with gonorrhea, the organism has been solely isolated from the throat. Pharyngeal infection also increases the risk of developing DGI during pregnancy.<sup>94</sup>

In order to prevent maternal complications and neonatal morbidity, all pregnant women and their sex contacts should be asked about past and present STD, counseled about the possibility of perinatal infections, and provided access to treatment, if needed. Furthermore, all women at risk (see risk factors above, however, these may vary in different settings) for gonorrhea or living in a high-prevalent setting should be screened during early pregnancy (first prenatal visit). Women found infected with gonorrhea during the first trimester should be promptly provided appropriate treatment and be retested within approximately 3–6 months, preferably in the third trimester. Furthermore, uninfected women who remain at high risk for gonorrhea should also be retested during the third trimester.<sup>24</sup> Notification and prompt treatment of sex contacts are imperative since reinfection has been reported in about 11–30% cases.<sup>95</sup>

## NEONATAL GONORRHEA

The most frequent manifestation is conjunctivitis (ophthalmia neonatorum).<sup>21</sup> The disease presents as a mucopurulent to purulent discharge that literally pours out when the eyelids are separated. Both the eyes are nearly always affected. The conjunctiva becomes intensely inflamed, bright red, and swollen with marked chemosis. There is dense infiltration of the bulbar conjunctiva initially that later becomes puckered and velvety with free discharge of pus, serum, and blood. A false membrane may form in a few cases resembling membranous conjunctivitis. Untreated cases

develop corneal ulcers over an oval area just below the centre of cornea. Rarely, oval marginal ulcers may form, followed by corneal perforation, iris prolapse, and extrusion of the lens. Other complications include anterior synechiae, adherent leukoma, partial or total anterior staphyloma, anterior capsular cataract, and panophthalmitis. Macular fixation may be impaired causing nystagmus. According to historical data, approximately 3% of neonates with untreated gonococcal ophthalmia neonatorum will develop complete blindness and 20% will develop some degree of corneal damage.

## GONORRHEA IN CHILDREN

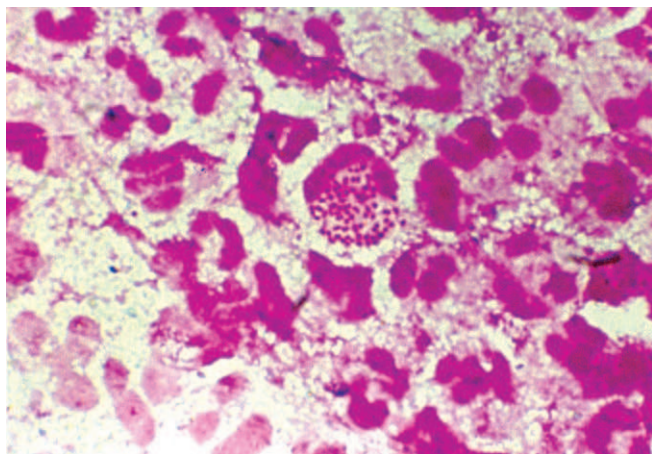
Gonorrhea is more common in girls than in boys. Sexual abuse is the most common cause of gonorrhea in children and, according to a report from 1994, reported rates of gonococcal infection from case series range from 3% to 20%.<sup>96</sup> Potential non-sexual causes include sharing of bed or towels with infected parents, use of infected thermometers or contaminated toilet articles in hospital wards and orphanages. However, this type of non-sexual gonorrhea transmission is extremely rare and there are only a couple of confirmed cases described in the scientific literature. The most common manifestation in girls is vulvovaginitis since the non-cornified vaginal mucosa in the prepubertal age group is most susceptible to infection. It presents as vaginal itching, crusting and minimal discharge (that stains the undergarments), dysuria, vulval erythema, and edema. Ascending infection leading to salpingitis and PID with pelvic abscess is very rare. In boys, gonococcal urethritis similar to that in adults occurs and is usually associated with anorectal and tonsillopharyngeal colonization. DGI in the forms of arthritis, meningitis, endocarditis, myocarditis, conjunctivitis, and hepatitis is exceedingly rare in this age group.

## Diagnosis of Gonorrhea

Diagnosis of gonorrhea based solely on clinical manifestations is very difficult and is only suggestive. Accordingly, laboratory diagnostics is crucial for provision of gonorrhea diagnosis.

The presumptive diagnosis of gonorrhea by identification of characteristic intracellular Gram-negative diplococci within PMNL in Gram-stained smears (Fig. 39.8) remains the mainstay in many clinical settings, particularly for patients with the signs and symptoms of gonorrhea. This method is also simple, rapid, and cheap. However, the method is only sufficient to provide a definitive diagnosis (presence or absence of infection) for urethral gonorrhea in symptomatic men (specificity [ $>99\%$ ] and sensitivity [ $>95\%$ ]). In asymptomatic men, due to the substantially lower sensitivity (30–50%), a negative Gram stain of a urethral smear is not sufficient for excluding the possibility of gonorrhea. This is also true for Gram stain of endocervical specimens (30–50% sensitivity), pharyngeal specimens, and rectal specimens (40–60% sensitivity in blindly obtained specimens), due to the low sensitivity and also a sub-optimal specificity (in particular for pharyngeal specimens). Accordingly, Gram stain should not be used as the sole test for diagnosis of gonorrhea





**Fig. 39.8:** Gram-stained smear of urethral discharge (male) showing Gram-negative intracellular diplococci within polymorphonuclear leukocytes.

in these specimens. In some settings, methylene blue staining of smears is used, which is a simple, rapid, and useful method where laboratory facilities are not well-developed. However, compared to Gram staining this method has a lower specificity.<sup>17–21,24,26,97</sup>

Laboratory diagnosis of gonorrhea by sensitive and specific detection of *N. gonorrhoeae*, or its nucleic acid, is strongly recommended. Culture diagnostics of gonorrhea (Fig. 39.9) has historically been the gold standard method due to, in particular, its high specificity (100%; i.e., if appropriate species verifying tests are utilized) but also high sensitivity (80–>95%; i.e., dependent on anatomic sites sampled and optimizations of entire procedure), and providing opportunities for phenotypic characterization. Importantly, culture of *N. gonorrhoeae* is the

only diagnostic method that allows testing of antimicrobial susceptibility, which is essential to monitor the emergence of resistance to current therapies. However, for a high sensitivity and specificity each step of the culture diagnostics requires to be optimized, including specimen collection, specimen transportation medium, and transportation (if bed side culture, which is ideal, is not performed), inoculation and incubation of cultures, and subsequent use of appropriate species verifying assays for *N. gonorrhoeae*. A selective culture medium, ideally combined with a non-selective medium, should be used. Many effective selective culture media have been developed, such as Modified Thayer–Martin (MTM), Martin–Lewis (ML), New York City (NYC) and GC-Lect (GC–L) medium, which are composed of GC agar base or equivalent media supplemented with growth factors and antimicrobial agents to inhibit growth of other bacteria or fungi. These selective media commonly include vancomycin (or lincomycin), colistin, nystatin (or amphotericin B), and trimethoprim to inhibit Gram-positive bacteria, non-gonococcal Gram-negative bacteria, fungi, and swarming *Proteus* species, respectively. Furthermore, appropriate species verification of *N. gonorrhoeae* should be performed, including identification of Gram-negative diplococci in microscopy, rapid oxidase production (Fig. 39.10), and at least one species verifying assay, such as carbohydrate utilization test (Fig. 39.11), rapid biochemical or chromogenic enzyme substrate tests, co-agglutination test (e.g., Phadebact Monoclonal GC Test) (Fig. 39.12), immunofluorescence assay (e.g., MicroTrak *N. gonorrhoeae* culture confirmation test) (Fig. 39.13), or molecular test (NAH test or NAAT).<sup>17–21,23,24,26,97</sup>

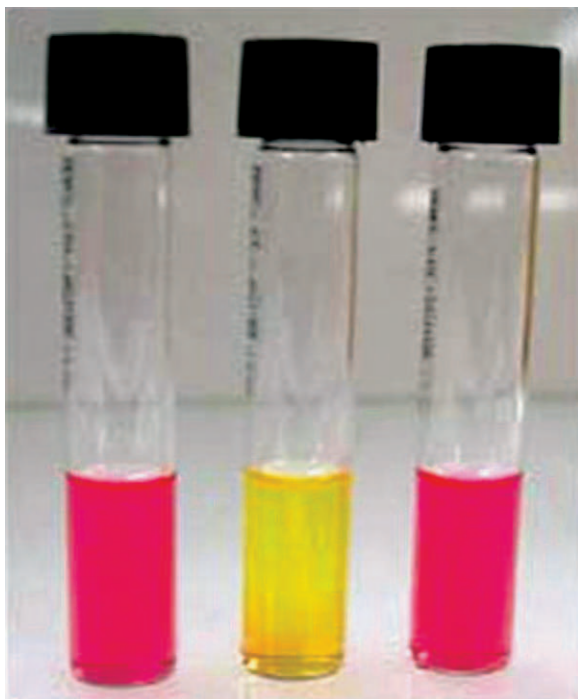
During the recent decades, molecular detection (NAH tests and, in particular, NAATs) for *N. gonorrhoeae* has been rapidly



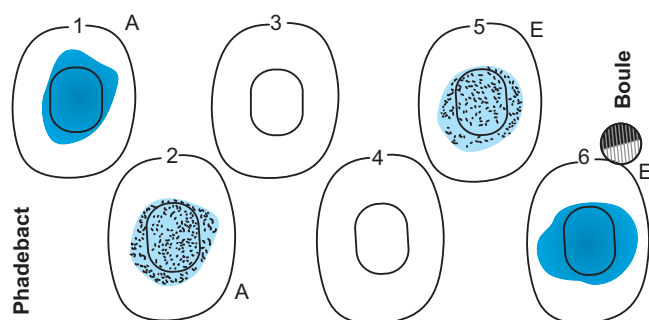
**Fig. 39.9:** Characteristic colonies of *Neisseria gonorrhoeae* grown on New York City culture medium.



**Fig. 39.10:** Rapid oxidase production of gonococcal colonies displayed directly on culture medium.

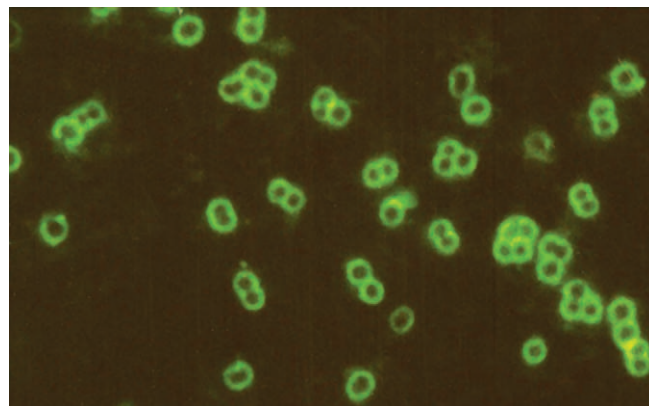


**Fig. 39.11:** Carbohydrate utilization test (Cystine Trypticase Agar [CTA] test) showing *Neisseria gonorrhoeae* degrading glucose (yellow) but not maltose (pink) or sucrose (pink).



**Fig. 39.12:** Co-agglutination test (Phadebact Monoclonal GC Test) of one *Neisseria gonorrhoeae* strain (no. 2, showing typical co-agglutination) and one *N. meningitidis* strain (no. 1, no co-agglutination). No. 5 and 6 are positive control and negative control, respectively.

replacing the culture diagnostics in many settings. Especially the NAATs offer highly sensitive and specific detection. The molecular tests are also more tolerant of delays or inadequacies in collection or transportation of specimens, more rapid, can be highly automated, and commonly can detect *N. gonorrhoeae* and *C. trachomatis* simultaneously. Furthermore, NAATs allow testing of also non-invasive specimens (including self-collected specimens), such as vaginal swabs and urine, while culture and NAH tests require invasive specimens, such as endocervical swab from women and urethral swab from men. There are many different NAATs commercially available, which use divergent



**Fig. 39.13:** Immunofluorescence assay (MicroTrak *N. gonorrhoeae* Culture Confirmation Test) showing characteristic fluorescent gonococci.

methods for amplification of a *N. gonorrhoeae* specific DNA or rRNA sequence, i.e., polymerase chain reaction (PCR; Roche diagnostics and Abbott Laboratories), strand displacement amplification (SDA; Becton Dickinson), and transcription-mediated amplification (TMA; Gen-Probe). The sensitivity of these NAATs in both urogenital and extragenital anatomic sites is superior to culture, but the performance characteristic, including sensitivity and specificity, varies with the type of NAAT assay.<sup>17,19,21–25,97–104</sup> No commercial NAAT is licensed by any regulatory body for detection of *N. gonorrhoeae* in rectal, pharyngeal, and conjunctival specimens. Nevertheless, as detection of the gonococci by NAATs usually is more sensitive compared to culture, some laboratories offer these tests for diagnosis of gonorrhea and some laboratories have also established their own performance specifications for using NAAT with rectal and pharyngeal swab specimens, thereby allowing results to be used for clinical management.<sup>24,97–101</sup> However, many of the gonococcal NAATs have been shown to cross-react with other non-gonococcal *Neisseria* species, e.g., *N. cinerea*, *N. flavescens*, *N. lactamica*, *N. subflava*, and *N. meningitidis*. These commensal *Neisseria* species and *N. meningitidis* can frequently inhabit extragenital sites, in particular oropharynx, and may result in false positive clinical reports. This sub-optimal specificity displayed by some of the NAATs may cause a very low positive predictive value (PPV), especially in setting with low prevalence of gonorrhea. Accordingly, laboratories that use NAATs for gonorrhea diagnostics, in particular if also extragenital specimens are examined, must ensure that specificity is not compromised by cross-reaction with non-gonococcal *Neisseria* species, and should sometimes consider to use an additional or supplemental assays to ensure definitive and confirmed diagnosis of gonorrhea.<sup>24,25,102–104</sup> The latest generation of gonococcal NAATs, however, displays a substantially higher specificity. It is also important to keep in mind that the results of the NAATs must be interpreted carefully in the context of diagnosis, due to the fact that *N. gonorrhoeae* DNA, which usually is eliminated 2–3 days after successful treatment, may in rare cases be present in specimens



for up to 2–3 weeks.<sup>17,26,105</sup> Because molecular tests (NAH tests or NAATs) cannot provide antimicrobial susceptibility results, in cases of suspected or verified clinical treatment failure, culture and antimicrobial susceptibility testing should always be included in the diagnostics. Other disadvantages with NAATs include the need for expensive equipment and diagnostic reagents, appropriate laboratory facilities and training, and the risk of contamination by previously amplified nucleic acid.<sup>17,19,21–26,97,102–104,106</sup>

## Antimicrobial Treatment of Gonorrhea

Effective treatment of gonorrhea is defined as the elimination of *N. gonorrhoeae* from all anatomic sites.<sup>107</sup> Single dose oral therapy has historically been preferred for high compliance and ease of administration. An antimicrobial recommended for first-line treatment of gonorrhea should treat >95% of the patients with uncomplicated urogenital and anorectal infection.<sup>5,26</sup> Due to the lack of adequate clinical studies for the currently used therapeutic options, nowadays the first-line antimicrobials are commonly recommended to be replaced when  $\geq 5\%$  of the gonococcal strains in the general population are resistant.<sup>5,26</sup> When initially introduced for treatment, many antimicrobial agents were highly effective against *N. gonorrhoeae*, wild type is inherently susceptible to many antimicrobials. However, during the last 70–80 years, *N. gonorrhoeae* has developed resistance to mainly all antimicrobials introduced for treatment of gonorrhea. In most cases, resistance has emerged and spread internationally only a few decades after introduction of the antimicrobial. Worryingly, the antibiotic treatment options now seem to be running out, and in near future gonorrhea may become untreatable in certain circumstances (see below).<sup>4,5</sup>

In general, antimicrobial resistance shows geographical variation, some antimicrobials have lower efficacy at extragenital sites (especially oropharynx), some are contraindicated under special circumstances, such as pregnancy or neonatal period and some are not affordable in less-resourced settings. Most of the old clinical trials were mainly studying treatment of uncomplicated urogenital gonorrhea. There are far less clinical data and also pharmacodynamic data available regarding the treatment of anorectal or pharyngeal infection, and there is a dearth of reports on the treatment outcome of complicated infection.

## DRUG TREATMENT AND RESISTANCE IN *N. GONORRHOEA*

### History

Before chemical and antimicrobial therapies were introduced, therapies such as urethral astringents, soundings, and mechanical devices were used for treatment of gonorrhea. In regard to chemical therapies, injection of mercury via the urinary meatus was used before urethral irrigation with potassium permanganate solution and the widely used silver nitrate were introduced in the late 1800s.<sup>27,108</sup> Protargol (a colloidal silver compound) was introduced in 1897, and it rapidly replaced silver nitrate. Protargol

was used mainly until the introduction of the first antimicrobials, i.e., the sulfonamides in 1936.<sup>27,28,109,110</sup> The sulfonamides were initially very effective. However, within 6–8 years, in some settings, >75% of the gonorrhea patients carried gonococci resistant to sulfonamides.<sup>27,28,109,110</sup> Fortunately, already in 1943 penicillin was shown to be highly effective for treatment of gonorrhea.<sup>29</sup>

### Penicillins

The introduction of penicillin for treatment of gonorrhea in 1943<sup>29</sup> led to virtual abandonment of sulfonamides and single, low-dose treatment with penicillin became the standard treatment. Remarkable cure rates were achieved, however, within 10–15 years a steady decrease in the penicillin susceptibility resulting in clinical treatment failures was observed.<sup>110</sup> The decreasing penicillin susceptibility was from the 1950s until the mid-1970s met by using escalating doses and combining penicillin with probenecid.<sup>111,112</sup> This gradual decrease in penicillin susceptibility was due to the sequential accumulation of chromosomal resistance mutations (see below).<sup>109</sup> The extended-spectrum penicillins, such as ampicillin, amoxicillin, ticarcillin, piperacillin, and mezlocillin, showed high activity against *N. gonorrhoeae*<sup>113</sup> and some of these (especially ampicillin and amoxicillin) were included in the regimens for treatment in many settings worldwide. In 1976, two types of  $\beta$ -lactamase encoding plasmids, originating in Asia and Africa, causing high-level penicillin resistance were reported in *N. gonorrhoeae*.<sup>34,35</sup> These  $\beta$ -lactamase producing strains spread internationally; however, they remained in low prevalence for several years in many geographical regions worldwide. Accordingly, it was mainly after the discovery and characterization of the first strain causing penicillin-resistant gonorrhea due to chromosomal mutations only<sup>109,114</sup> and the subsequent spread of these strains that penicillin was abandoned as first-line treatment. For instance, surveillance data from the USA in 1989 reported significant and sustained resistance to all the penicillins, and these were no longer recommended.<sup>115</sup> At present time, the level of resistance to penicillins is high in most countries worldwide.<sup>3,5</sup> Already in the late-1940s to 1960s other antibiotics were used in the treatment of gonorrhea for those patients where penicillin was contraindicated; these alternative antibiotics included certain aminoglycosides and tetracycline.

### Tetracyclines

Tetracyclines have been important and effective antimicrobial agents in the treatment of several STDs, and previously these were also used for treatment of gonorrhea in many countries. However, tetracycline resistance, both chromosomally and plasmid mediated, emerged and rapidly spread internationally, and is nowadays high in most countries worldwide.<sup>3,5</sup> In the USA and Western Europe, tetracyclines have not been recommended for treatment of gonorrhea since the late-1980s.



## Spectinomycin

Spectinomycin (an aminocyclitol) played a central role in the control of gonococcal infection following emergence of PPNG and high-level chromosomally mediated penicillin resistance.<sup>114</sup> It was shown effective in clinical trials, curing 98.2% of uncomplicated urogenital and anorectal gonococcal infections (single intramuscular [IM] dose of 2 g), and safe in pregnancy. However, spectinomycin has poor efficacy against pharyngeal infection (51.8%; 95% CI = 38.7–64.9%).<sup>24,107</sup> Spectinomycin was used as first-line treatment for the USA military personnel in Korea and the gonococci quickly developed resistance.<sup>116</sup> Nevertheless, spectinomycin resistance seems unstable, reverts once its use is discontinued and consequently at present time spectinomycin resistance is rare worldwide.<sup>3–5</sup> Unfortunately, spectinomycin, which would be valuable for treatment of patients who cannot tolerate cephalosporins and cephalosporin-resistant gonorrhea, is not available in many settings worldwide.

## Fluoroquinolones

Fluoroquinolones became popular and proved effective as first-line treatment from the mid-1980s or early-1990s, and onwards in many countries. They were also effective in eradicating anorectal and pharyngeal infection, and safe in individuals allergic to  $\beta$ -lactam antimicrobials. However, the fluoroquinolones are contraindicated for use in pregnancy, children, and growing adults. Ciprofloxacin has been the most widely used fluoroquinolone, but also ofloxacin has been commonly administered in many countries. A single oral dose of 500 mg ciprofloxacin was well-tolerated and very effective. Ofloxacin 400 mg orally in a single dose and norfloxacin given in a single dose of 800 mg were also effective.<sup>117</sup> Unfortunately, clinically resistant strains emerged, they were transmitted in South-East Asia already in the mid-1990s,<sup>118</sup> and soon they were spreading worldwide. Due to the high prevalence of ciprofloxacin resistance, many Asian and European countries excluded ciprofloxacin as first-line treatment in the early- or mid-2000s. By 2007, fluoroquinolone-resistant strains were of such high prevalence throughout the USA that all fluoroquinolones were removed from the recommended treatment regimen.<sup>109,119</sup> At present time, the level of ciprofloxacin resistance is high in most countries worldwide, i.e., where adequate surveillance has been performed.<sup>3,5</sup>

## Azithromycin

Azithromycin is a relatively new macrolide (azalide class). The oral dose of azithromycin displays a higher absorption as compared to the previously used erythromycin due to its greater stability in the gastric acid, and so it achieves a higher and more sustained intracellular concentration. A single 1 g oral dose of azithromycin is an effective and frequently recommended therapy against urogenital *C. trachomatis* infection.<sup>24</sup> According to a recent review, using single dose azithromycin therapy has also shown aggregated cure rates for urethral and endocervical gonorrhea

of 96.5% for a 1 g dose and 99% for a 2 g dose. Furthermore, azithromycin cured 97.9% cases of oropharyngeal infection and 97.1% cases of anorectal infection evaluated within these clinical trials.<sup>120</sup> However, several studies have documented treatment failures using 1 g of azithromycin and emergence of resistance may be more rapid using this lower dose.<sup>121–123</sup> The disadvantages of using azithromycin for treatment of gonorrhea include its cost, high frequency of gastrointestinal side-effects (but these are less frequent with the new formulation of azithromycin available in some countries), and in particular the fear of rapid development of resistance. The resistance level has also increased rapidly and high-level azithromycin-resistant gonococcal isolates have been identified in several countries.<sup>5</sup> Due to this concern regarding rapid emergence of resistance, widespread or first-line use of azithromycin as sole antimicrobial therapy for gonorrhea has never been recommended. However, azithromycin can be valuable for treatment of gonococcal infections from any site in persons with severe allergic reactions to  $\beta$ -lactam antimicrobials, in some other specific clinical situations and in combination therapy, i.e., with extended-spectrum cephalosporins in the treatment of both gonorrhea and *C. trachomatis* infection and possibly in future combination therapy for ceftriaxone-resistant gonorrhea.

## Cephalosporins

Extended-spectrum cephalosporins have, in several decades, proved highly efficacious for treatment of urogenital, anorectal, and pharyngeal gonorrhea worldwide. The injectable ceftriaxone or oral cefixime are the most potent and usually recommended extended-spectrum cephalosporins for treatment of gonorrhea.<sup>3–5,24</sup>

Ceftriaxone, because of its high intrinsic potency, long half-life (6–9 hours) and lack of resistance in circulating gonococcal strains, is currently the most potent gonorrhea antimicrobial for a single dose regimen.<sup>3,5,24</sup> Clinical experience has shown that ceftriaxone is safe, including in pregnancy and neonates, and effective for the treatment of gonorrhea at any anatomic site, displaying cure rates of 99.2% for uncomplicated urogenital and anorectal, and 98.9% for pharyngeal infections in clinical trials.<sup>24,107,124</sup> Alternative parenteral single-dose regimens for urogenital and anorectal gonorrhea include ceftizoxime 500 mg IM, cefoxitin 2 g IM with probenecid 1 g orally, or cefotaxime 500 mg IM.<sup>24,125</sup> However, none of these injectable cephalosporins offer any advantages over ceftriaxone for urogenital and anorectal infection, and efficacy for pharyngeal infection is less certain.<sup>24,107,124</sup> The main drawback with ceftriaxone is its high cost in several settings and parenteral mode of administration.

Cefixime is an oral preparation with similar spectrum as ceftriaxone and a single 400 mg oral dose has been shown to be nearly as effective as the injectable ceftriaxone against uncomplicated urogenital and anorectal gonorrhea. However, cefixime (400 mg oral dose) does not provide as high, nor as sustained, a bactericidal level as that provided by ceftriaxone (250 mg IM dose). In clinical trials, cefixime (400 mg oral dose) cured 97.5% of uncomplicated urogenital and anorectal (95% CI = 95.4–99.8%), and only 92.3% of pharyngeal gonococcal

infections (95% CI = 74.9–99.1%).<sup>24,107,124,126,127</sup> Accordingly, especially for some cases of pharyngeal gonorrhea cefixime (400 mg oral dose) may be sub-optimal.

Worryingly, in recent years susceptibility to these recommended first-line antimicrobials, i.e., ceftriaxone and cefixime, has decreased globally.<sup>3–5</sup> Cefixime treatment failures have been verified in Japan since several years,<sup>4,5,128,129</sup> and recently the first clinical failures were confirmed in Europe.<sup>130</sup> Given history, it is most likely that cefixime resistance will continue to spread globally and also ceftriaxone will have the same fate. Previously, only three cases of treatment failures of pharyngeal gonorrhea using ceftriaxone have been verified,<sup>131,132</sup> but these clinical failures were most likely affected by the known difficulties in treating pharyngeal gonorrhea compared with urogenital infection. Due to pharmacodynamic parameters, few (if any) antimicrobial agents can reliably cure all cases of pharyngeal gonorrhea infections.<sup>5,107,124,131</sup> Nevertheless, recently the fear of emergence of ceftriaxone resistance in *N. gonorrhoeae* was justified with the emergence and detailed characterization of the first gonococcal strain displaying high-level clinical resistance to ceftriaxone (MIC of 2–4 µg/mL), identified in Japan.<sup>4</sup> This is particularly worrisome as ceftriaxone is the last remaining option for empirical first-line treatment of gonorrhea. *N. gonorrhoeae* seems to be evolving into a true “superbug” and, gonorrhea may become untreatable in certain circumstances and especially in some settings.

## Future Management of Gonorrhea

A serious public health problem in which case gonorrhea may become untreatable in certain circumstances and, in particular, some settings may be approaching. To at least restrain the spread of cefixime and ceftriaxone resistance, timely public health multi-disciplinary and multi-component actions are imperative. A recent expert review described WHO initiatives to antimicrobial resistance containment and how to meet the public health challenges of emergence and spread of multi-drug resistant (MDR) *N. gonorrhoeae*, extensively-drug resistant (XDR) *N. gonorrhoeae*, and untreatable gonorrhea.<sup>5</sup> WHO has also recently launched a global gonococcal antimicrobial susceptibility programme (WHO Global-GASP), for enhanced and quality assured monitoring of antimicrobial resistance in *N. gonorrhoeae* worldwide.<sup>5,133</sup> However, all these actions will likely not be able to prevent the emergence, establishment and spread of cefixime and ceftriaxone resistance, but only delay the global spread of the resistance. Ultimately, a major focus important for public health globally is to timely develop new effective drugs (for single or combined use) and/or novel strategies for the treatment of gonorrhea, and ideally an effective vaccine.<sup>4,5</sup>

## Molecular Mechanisms for Resistance to Relevant Antimicrobials in *N. gonorrhoeae*

The resistance of *N. gonorrhoeae* to many antimicrobials, acquired by intrastrain mutations and/or interstrain transfer of DNA

by conjugation or transformation, is widespread and occurs as chromosomally mediated resistance to a variety of antibiotics and high-level plasmid-mediated resistance to penicillins and tetracyclines. The chromosomally mediated resistance usually develops slower and, for several antibiotics, this resistance is due to the cumulative effects of different mutations that decrease the affinity of the antimicrobial for its target molecule, increase the efflux of antimicrobials through efflux pumps, and/or decrease the intake of antimicrobials.<sup>5,26</sup>

### Penicillin Resistance

**Chromosomally Mediated Resistance** Gonococcal strains that require ≥2 mg/L of penicillin for inhibition and do not produce β-lactamase are designated as chromosomally mediated penicillin-resistant *N. gonorrhoeae* (CMRNG). This type of resistance is caused by the stepwise cumulative effects of mutations at multiple loci, including *penA* (mutations cause a decreased affinity of penicillin for its lethal target, the encoded penicillin binding protein 2 [PBP2]), *mtrR* promoter or coding region (mutations cause an overexpression of the MtrCDE efflux pump, which actively pumps the antimicrobial out of the cell), and *porB1b* (the “*penB*” resistance determinant that causes a decreased intake of antimicrobial through the porin PorB). In addition, one specific mutation in *ponA* causes a decreased affinity of penicillin for the encoded PBP1 (second target for penicillin), and further decreased susceptibility to penicillin. Moreover, the *penC* (currently named *pilQ2*) mutation in the *pilQ* gene, which encodes the secretin PilQ of the type IV pilin, inhibits the entry of penicillin in the bacterial cell and, accordingly, further decrease the susceptibility to penicillin. However, *pilQ2* mutations impact proper piliation, which is important for gonococcal disease and transmission of infection, and accordingly this mutation may not be of importance for wide spread of clinical penicillin resistance. Finally, at least one additional, non-transformable resistance determinant exists, the so-called “Factor X.”<sup>4,5,109,134–136</sup>

**Plasmid-Mediated Resistance** The high-level resistance to penicillin in PPNG is attributed to the production of the enzyme β-lactamase (penicillinase) via single-step acquisition of β-lactamase encoding plasmids (see above). β-lactamase hydrolyses the cyclic amide bond in the β-lactam ring of β-lactamase instable penicillins, converting the penicillin into inactive penicillinoic acid.

### Spectinomycin Resistance

Specific single nucleotide polymorphisms (SNPs) in the *16S rRNA* gene, which result in a decreased affinity of spectinomycin for its 16S rRNA target, mediate high-level resistance to spectinomycin.<sup>137</sup>

### Fluoroquinolone Resistance

The high-level resistance in quinolone-resistant *N. gonorrhoeae* (QRNG) is due to cumulative effect of multiple mutations in specific regions (quinolone resistance determining regions

[QRDR]) of the *gyrA* and *parC* genes that encode the subunits GyrA and ParC of the target enzymes DNA gyrase and topoisomerase IV, respectively.<sup>109,138</sup>

### Macrolide Resistance

Resistance to azithromycin and/or erythromycin can be caused by mutations in the *mtrR* promoter or coding sequence (result in an overexpression of the MtrCDE efflux pump), presence of the *mef* (*A*) encoded efflux pump (enhances the efflux of macrolides), presence of one or several *erm* genes encoding 23S rRNA methylases (modify the ribosomal target), or specific SNPs in one or several of the four genomic alleles encoding 23S rRNA (reduce the affinity of the macrolide for its ribosomal target).<sup>109,139</sup> The exceedingly high-level azithromycin resistance recently identified in some countries has been due to specific SNPs in several of the four alleles of the 23S rRNA gene.<sup>5,123,140</sup>

### Cephalosporin: Decreased Susceptibility and Resistance

The  $\beta$ -lactamase produced by PPNG, which degrades penicillins, is not affecting the extended-spectrum cephalosporins and fortunately *N. gonorrhoeae* has yet not developed or acquired any extended-spectrum  $\beta$ -lactamase (ESBL). Accordingly, the decreased susceptibility and resistance to extended-spectrum cephalosporins in *N. gonorrhoeae* are chromosomally mediated, and the mechanisms are similar to the mechanisms causing chromosomally mediated resistance to penicillins (see above). The most common mechanism in *N. gonorrhoeae* for decreased susceptibility or resistance to extended-spectrum cephalosporins is *penA* alteration, i.e., acquisition of a *penA* mosaic allele or A501 alterations in PBP2. However, the effects of different *penA* mosaic alleles on the susceptibility to extended-spectrum cephalosporins substantially differ and many new *penA* mosaic alleles are emerging. Mutations in the promoter and/or coding sequence of *mtrR* cause an over-expression of the MtrCDE efflux pump system, which further decreases susceptibility to the extended-spectrum cephalosporins. The *penB* resistance determinant (see above) results in additionally decreased susceptibility to the extended-spectrum cephalosporins. Alterations in PBP1 and PilQ (involved in chromosomally mediated penicillin resistance) do not seem to substantially affect the susceptibility to the extended-spectrum cephalosporins in presently circulating strains. Finally, at least one additional, non-transformable resistance determinant exists, the so-called "Factor X."<sup>4,5,109,134–136,141</sup>

### CURRENTLY RECOMMENDED TREATMENT REGIMENS FOR GONORRHEA

The recommended treatment regimens for uncomplicated gonorrhea according to the Sexually Transmitted Diseases Treatment Guidelines, 2010 from CDC, USA<sup>24</sup> and the 2009 European (IUSTI/WHO) guidelines on the diagnosis and treatment of gonorrhea in adults<sup>127</sup> are summarized in Table 39.2.

**Table 39.2:** The Recommended Treatment Regimens for Uncomplicated Gonococcal Infections According to the Sexually Transmitted Diseases Treatment Guidelines, 2010 from CDC, USA<sup>24</sup> and the 2009 European (IUSTI/WHO) Guidelines<sup>127</sup>

#### Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum in Adults and Adolescents

##### Recommended regimens

**Ceftriaxone** 250 mg in a single intramuscular (IM) dose<sup>24,127</sup>

OR (IF NOT AN OPTION<sup>24</sup>)

**Cefixime** 400 mg in a single oral dose<sup>24,127</sup>

OR

**Cephalosporin regimens** in a single injectable dose<sup>24,a</sup>

**Spectinomycin** 2 g in a single IM dose<sup>127</sup>

**PLUS<sup>24,127,b</sup>**

**Azithromycin** 1 g in a single oral dose

OR

**Doxycycline** 100 mg a day for 7 days

#### Uncomplicated Gonococcal Infections of the Pharynx

##### Recommended regimens

**Ceftriaxone** 250 mg in a single IM dose<sup>24,127</sup>

**PLUS<sup>24,b</sup>**

**Azithromycin** 1 g in a single oral dose

OR

**Doxycycline** 100 mg a day for 7 days

<sup>a</sup>Other cephalosporin regimens in a single injectable dose that are safe and effective include ceftizoxime 500 mg IM; cefoxitin 2 g IM, administered with probenecid 1 g orally; or cefotaxime 500 mg IM. However, none of these injectable cephalosporins offer any advantages over ceftriaxone for urogenital or anorectal infection, and efficacy for pharyngeal infection is less certain.<sup>24,107,124</sup>

<sup>b</sup>Treatment for gonorrhea should routinely be followed with effective treatment for concomitant *C. trachomatis* infection unless a sensitive diagnostic test has excluded co-infection.<sup>127</sup>

For alternative treatment regimens, treatment of gonococcal ocular infection (conjunctivitis in adults and ophthalmia neonatorum), disseminated gonococcal infection (DGI), salpingitis, and pelvic inflammatory disease (PID), see references 24 and 127.

### FOLLOW-UP AFTER TREATMENT

Partner notification is recommended for evaluation and treatment of sexual contacts. Test of cure is not recommended routinely for patients with uncomplicated gonorrhea who have been treated with recommended regimen(s). However, persons with persistent symptoms or whose symptoms recur shortly after treatment with a recommended regimen should be reevaluated by culture for *N. gonorrhoeae*; positive isolates should undergo antimicrobial susceptibility testing.

### Prevention of Gonorrhea

The first effective prophylaxis against gonococcal infection was described in 1881 by Karl Credé, who administered silver nitrate eye drops to neonates to prevent ophthalmia neonatorum.<sup>142</sup> No effective vaccine for gonorrhea has so far been developed, despite 3–4 decades of research in which whole organisms, purified components: pilus, transferring-binding proteins (TbpA/B), PorB-enriched outer membrane, etc., and some recombinants proteins



(PorB, including purified from Rmp-negative gonococci) have been evaluated as potential vaccine candidates. Major concerns have been raised regarding the mostly local, relatively low and unpersistent immune response after uncomplicated gonorrhea, i.e., poor protection causing possibilities of reinfection even with the identical gonococcal strain. The major concerns regarding the development of an effective gonococcal vaccine include (i) generation of non-bactericidal blocking antibodies (e.g., against Rmp) that block binding and activity of bactericidal antibodies (e.g., against PorB and LOS); (ii) sialylation of *N. gonorrhoeae* that facilitates binding of alternative complement regulator, factor H; (iii) possible elicitation of gonococcal IL-17 responses that suppress Th1/Th2 adaptive immune responses to natural infection; (iv) high level of antigenic heterogeneity in *N. gonorrhoeae*, the rapid antigenic variability, and phase variations (on/off switching) in the expression of, e.g., pili, Opa proteins and LOS; and (v) lack of an ideal animal model for this human specific pathogen (but novel transgenic mice expressing human genes required for gonorrhea should enable future vaccine research).<sup>55,143,144</sup> A polyvalent vaccine containing multiple antigenic epitopes of a single or several molecules may be needed. By using the new approach of “reverse vaccinology” not previously described conserved and immunogenic outer membrane proteins that can be potential vaccine candidates may also be identified based on the available *N. gonorrhoeae* genomes.

At present time, to reduce the incidence of gonorrhea, effective and accessible diagnostics; antibiotic treatment and contact tracing; screening for asymptomatic individuals; surveillance of the epidemiological characteristics and especially the antibiotic susceptibility of the bacteria, and the affected populations or sub-population (to identify risk behaviors and risk groups), to develop improved control measures and interventions are crucial. In addition, widespread education concerning sex, the transmission of infection, and the importance of use and availability of condoms that may result in changed and more protected sexual behavior is important, as are targeted preventions and interventions for high-risk groups.

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# Chlamydia Trachomatis Infections

Nicola Steedman

# 40

## Introduction

*Chlamydia trachomatis*, a small gram-negative intracellular bacterium, is the most common bacterial sexually transmitted infection worldwide in the present day.<sup>1</sup> It can infect both men and women and produces no symptoms in a proportion of hosts hence providing an ongoing reservoir for continued infection.<sup>2</sup> Chlamydial infections can, however, have serious consequences for the host. In man *Chlamydia trachomatis* is the leading cause of preventative blindness on a global scale through the disease known as trachoma.<sup>3</sup> In its sexually transmitted form *C. trachomatis* infection causes urethritis and epididymo-orchitis in man and it is a leading cause of pelvic inflammatory disease, ectopic pregnancy, and infertility in women.<sup>4,5</sup> In addition, chlamydial infection can be passed from mother to neonate during parturition causing nongonococcal ophthalmia neonatorum and pneumonia.<sup>6</sup> Chlamydial conjunctivitis may in fact be found in all age groups and chlamydial proctitis can occur in both men and women as a result of anal intercourse.<sup>7</sup>

The relatively late isolation and identification of this organism is a result of its intracellular lifecycle and historically has impeded knowledge about and research into this important pathogen.

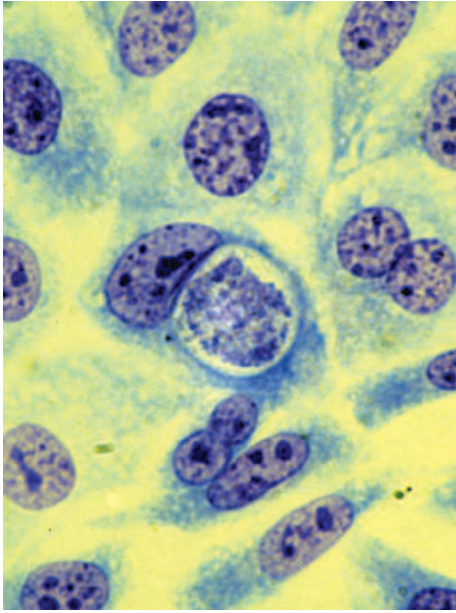
## History

Sexually transmitted diseases were initially considered more as clinical syndromes rather than caused by specific individual organisms and the discovery of *C. trachomatis* was prompted more by exclusion than anything else. Following the successful identification of the organism *Neisseria gonorrhoeae* in the late 19th century, it became apparent that urethritis in men and conjunctivitis in neonates occurred when *N. gonorrhoeae* was not present, suggesting the existence of other causative organisms.<sup>8</sup> Chlamydial intracellular inclusions were noted during light microscopy of clinical specimens from the 1900s and the lymphogranuloma venereum (LGV) organism was recognized first, however it was not until the late 1950s that *C. trachomatis* biovar *trachoma* was successfully isolated.<sup>9</sup> This was at least in part a result of the fact that *C. trachomatis* cannot be cultured

by conventional methods and required the development of a culture system involving yolk sac inoculation of embryonated hens' eggs.<sup>10</sup> The subsequent evolution of laboratory cell culture methods allowed more widespread testing of clinical specimens and prompted the suggestion that the organism was a cause of nongonococcal urethritis (NGU) in men. Studies in the 1970s confirmed isolation rates of around 50% in men with NGU compared with less than 5% in control subjects and concordance was established with sexual partners, confirming sexual transmission of *C. trachomatis* and its likely etiological role in NGU.<sup>1,11</sup>

It was originally thought by some that *C. trachomatis* must be a virus as it was discovered to be filterable and to be an obligate intracellular pathogen for its replication. It was, however, Sir Samuel Bedson and coworkers who correctly identified bacteria-like binary fission as the mechanism of chlamydial replication and reclassified the organism as bacterial. It was Bedson who isolated and characterized *Chlamydia psittaci* as the agent of psittacosis in the early 1930s and chlamydial organisms were known as Bedsonia initially in recognition of this work.<sup>12</sup> Subsequent titles for the *Chlamydia* genus included the psittacosis-lymphogranuloma-trachoma group (PTL organisms) and the trachoma-inclusion conjunctivitis organisms (TRIC group) before three separate species of *Chlamydia* were recognized within the genus: *C. psittaci*, *C. pneumoniae*, and *C. trachomatis*. The word chlamys comes from the Greek, meaning "cloak draped around the shoulder." This describes how the intracytoplasmic inclusions caused by the bacterium are "draped" around the infected cell's nucleus (Fig. 40.1).

In 1999 the single genus, *Chlamydia*, was reclassified into two different genera; *Chlamydia* and *Chlamydophila* (Fig. 40.2).<sup>13</sup> In addition to genetic and protein sequence differences with the genus *Chlamydia*, *Chlamydophila* spp. do not produce detectable glycogen and have one ribosomal operon whereas *Chlamydia* spp. have two. As a result of the chlamydial reclassification five new species were validated and the former *C. pneumoniae*, *C. pecorum*, and *C. psittaci* were moved to the new genus *Chlamydophila*. In this way the genus *Chlamydia* now consists of three species. The



**Fig. 40.1:** Cell infected with *Chlamydia trachomatis* showing classic perinuclear 'draped' inclusion body.

first of these is *Chlamydia trachomatis* (comprising the two human biovars: trachoma and LGV). The mouse and swine strains that were previously grouped with this species now belong to separate species (*C. muridarum* and *C. suis*, respectively).

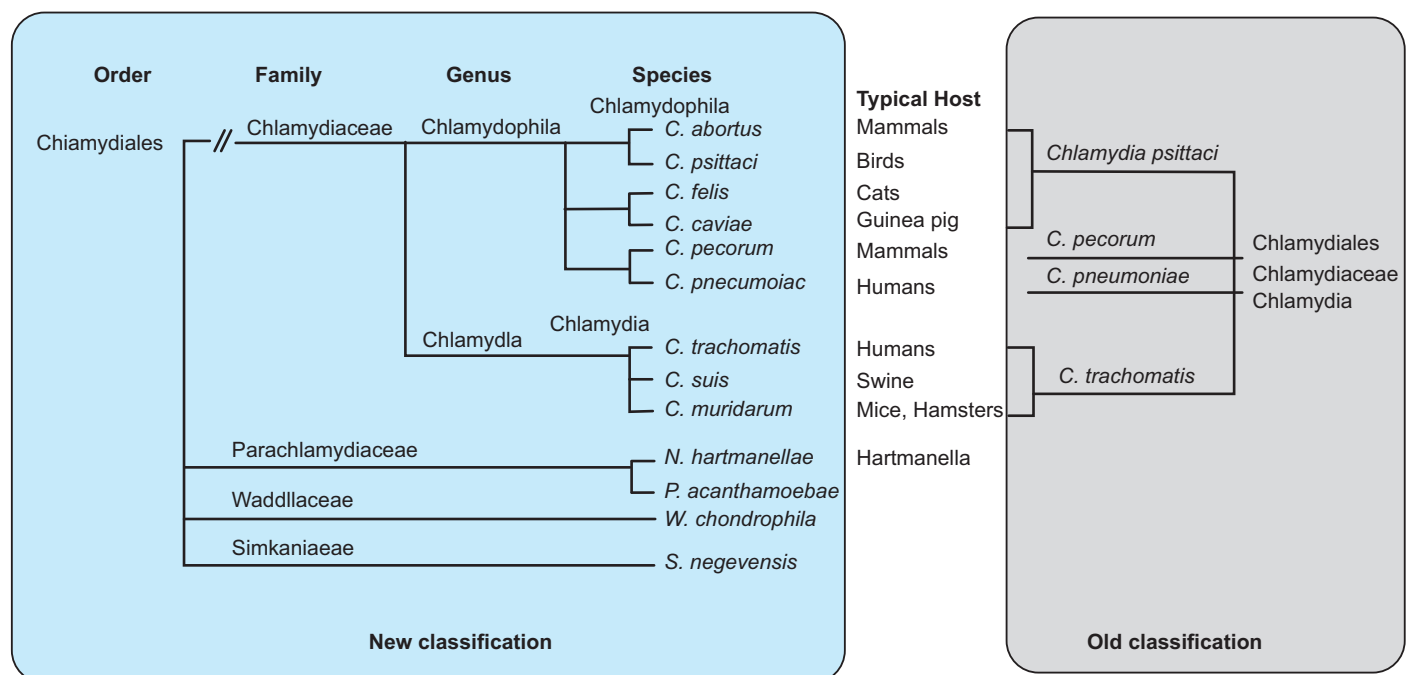
The genus *Chlamydophila* consists of six species. The first of these is *Chlamydophila psittaci*, which primarily infects birds.

The former 'mammalian' *Chlamydia psittaci* abortion, feline, and guinea-pig strains have now been reclassified as three new species (*C. abortus*, *C. felis*, and *C. caviae*). The species *Chlamydia pecorum* has been renamed *Chlamydophila pecorum*. *C. pecorum* strains are generally noninvasive in a mouse model of virulence and are serologically and pathogenically diverse, having been isolated only from mammals. Finally *Chlamydia pneumonia* has been reclassified as *Chlamydophila pneumoniae*. Although it was formerly thought to be a specific human pathogen, it is now thought that *C. pneumoniae* can infect horses, koala, and other animals.<sup>14</sup>

## Biology

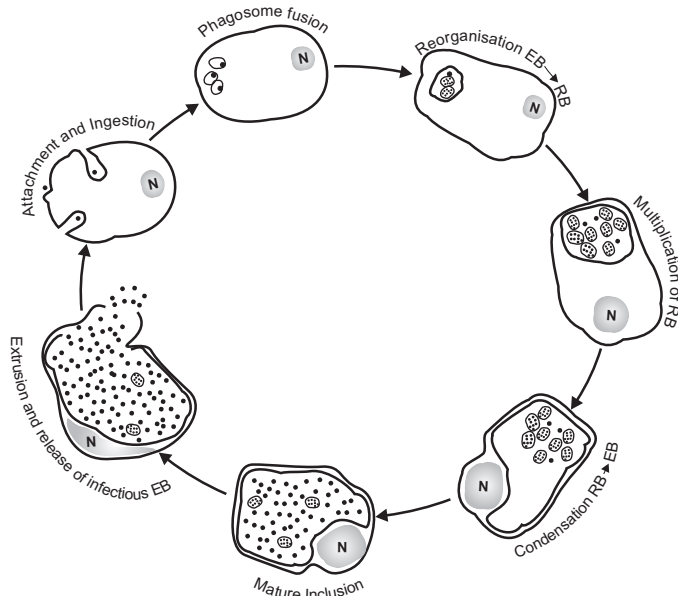
*C. trachomatis* is a gram-negative bacterium which exists as an obligate intracellular parasite with a lifecycle consisting of two distinct phases with two morphological forms. In the first of these the organism exists as small elementary bodies (EB) which are the infectious form of the bacterium. EB attach to cells and enter them before changing into the more metabolically active form, the reticulate body (RB). The larger RB is responsible for replication of the organism and the intracellular inclusions that can be seen under light microscopy. Following replication by binary fission, RB change morphologically back to EB which are finally released from the cell as new infectious agents (Fig. 40.3).

EB are spherical structures approximately 200–350 nm in diameter which closely adhere to the host cell surface and attachment appears to be aided by heparin sulfate-like molecules.



**Fig. 40.2:** Chlamydial taxonomy. The 1999 reclassification. Adapted from: Bush RM and Everett KDE. Molecular Evolution of the Chlamydiaceae. *Int J Syst Evol Microbiol* 2001;51:203–20.





**Fig. 40.3:** Life cycle of *Chlamydia trachomatis*. EB, elementary body; RB, reticulate body.

Endocytosis is the mechanism by which the EB enters the cell and although specific cell surface receptors responsible for this process have not yet been elucidated, various EB surface structures have been purported to be involved including major outer membrane proteins (MOMP) and in particular the cysteine-rich protein OmcB.<sup>15,16</sup> The endocytic process appears to involve elements of both phagocytosis and pinocytosis and results in the internalization of the EB within a cell membrane lined vesicle within the cell cytoplasm. Although the vesicles pass through the usual early maturation stages to become early endosomes and late endosomes, it appears that the expression of chlamydial gene products prevents subsequent fusion with lysosomes and therefore protects the endosome from lysis. Instead of fusing with lysosomes, the chlamydial endosome intersects vesicles destined for the exocytic pathway while chlamydial particles within undergo the process of morphological change from EB into RB.<sup>16</sup> This change occurs within 6–9 hours of chlamydial ingestion by the cell and is marked by the notable increase in size of the cellular inclusion body. RB are larger (1000 nm diameter) particles than EB and essentially are structurally gram-negative bacteria. They proceed to multiply by binary fission producing RNA, DNA, and protein while the chlamydial endosome is tracked, potentially via microtubules, to the cellular Golgi apparatus. Within 36 hours the lifecycle is complete. The metabolically active RBs which cannot survive in an extracellular environment have reorganized to the EB form and the cellular chlamydial inclusion has fused with the cell membrane to release new infectious particles of *C. trachomatis*.

In the process of infection and replication *C. trachomatis* appears to disrupt normal cellular function very little and the organism appears to require little from the host cell to support its replicative cycle. *C. trachomatis* does, however, appear to require

host ATP and does not appear to generate its own energy sources in its metabolically active RB state.<sup>17</sup> It evades immune detection by avoiding intracellular processing and remaining intact within endocytic vesicles where it completes its entire lifecycle. It appears too that cells infected with *C. trachomatis* are also resistant to apoptosis though the mechanism involved remains unclear.<sup>18</sup> Despite these observations it is apparent that chlamydial infection can be naturally cleared by some hosts, though reinfection is subsequently possible. In others *C. trachomatis* establishes a persistent infection although the correlates with clearance and persistence are as yet unresolved.<sup>19–23</sup>

## Biovars and Serovars of *C. trachomatis*

*C. trachomatis* has been classified into serovars which are associated with distinct type-specific antigens on the surface of EB and which result in specific clinical syndromes.<sup>24</sup>

*Chlamydia trachomatis* biovar *trachoma*, serovars A, B, and C are associated with hyperendemic or tropical trachoma. This disease is a leading cause of blindness in developing countries and is transmitted by ocular discharge.<sup>25</sup> In contrast, *C. trachomatis* biovar *trachoma* serovars D to K cause genital tract chlamydial infections. These serovars can also affect the eye and are responsible for adult chlamydial conjunctivitis and conjunctivitis in newborn babies. Finally *C. trachomatis* biovar *lymphogranuloma venereum* (LGV) serovars L1–L3 causes a separate group of clinical syndromes.<sup>26</sup> This biovar differs from the squamocolumnar-infecting trachoma biovar in that it causes disease of the genital lymphatic tissue and therefore may present with lymph node masses or a symptomatic proctitis resembling inflammatory bowel disease.

## Epidemiology

Genital *C. trachomatis* remains the most common bacterial STD in the developed world.<sup>27,28</sup> In 2008, there were an estimated 200,959 diagnoses of genital chlamydial infection made across all clinical settings in the UK and more than 1.5 million cases are reported annually in the USA.<sup>29,30</sup>

Overall prevalence figures vary, but a recent study of nearly 15,000 young Americans suggested a prevalence of 4.2% with higher rates in women and the highest in African American women where the prevalence reached 14%.<sup>31</sup> Elsewhere in the world *C. trachomatis* prevalence is also very variable. A study from Paris of women attending private gynecology appointments showed a prevalence of only 0.8% overall with a higher prevalence of 5.2% in younger women (less than 21 years old).<sup>32</sup> A study from Thailand reported 5.7% prevalence in pregnant women and one of the highest prevalence estimates (28.5%) has been found in female sex workers in Dakar.<sup>33,34</sup>

Over the past 10 years, diagnoses have risen steadily in men and women across all age groups but the rise has been most pronounced in women aged less than 25 years and men aged 20–24.<sup>35</sup> Young age is one of the strongest predictors of chlamydial infection with various hypotheses proposed to explain this.<sup>19</sup> Sexual behavior is likely to play a large role, however it has also

been suggested that physiological specifics of the immature cervical mucosa may make it more susceptible to infection.<sup>36</sup> It remains theoretical too that advancing age may afford some degree of immunity to clinical infection following repeated previous exposures.<sup>19</sup> The highest rates of *C. trachomatis* diagnosis in the UK are certainly still seen in 16–19 year old women and 20–24 year old men; however rates are higher in women than men in all age groups.<sup>35</sup> Gender statistics need to be interpreted with some caution however as rising rates of reported chlamydial infection are likely to be at least in part a result of increased screening for the organism using more sensitive tests. In addition, opportunistic screening inevitably happens more frequently in women as they present for cervical smear testing and contraceptive reviews, hence estimates of *C. trachomatis* infection in men may be falsely low. In the United States of America prevalence in 18–26 year old men has been reported as 3.7% with rates highest again in those with African American heritage (11%).<sup>31</sup> A study of nearly 1500 adolescent high school males found a higher overall prevalence of 6.8% for *C. trachomatis* infection and data from the National Health and Nutrition Examination Survey of the USA (1999–2002) suggest that rates of chlamydial infection are higher in black and Hispanic men and those in prison or other correctional institutions.<sup>37,38</sup> Additional studies have confirmed chlamydial infection to be more frequent in ethnic minorities and those incarcerated.<sup>39,40</sup> *Chlamydia trachomatis* prevalence studies in men are often conducted in military settings and allow some limited geographical comparisons. A study from four American military bases suggested a *C. trachomatis* prevalence of 4.1% among male recruits, however higher estimates have been reported from similar patient populations from Scotland (9.8%) and Stockholm (10%).<sup>41–43</sup>

The prevalence of *C. trachomatis* in pregnant women has been reported to vary from 2% to 20% in different study populations, with all studies finding the highest prevalence in younger pregnant women.<sup>44,45</sup> A UK cohort study estimated an overall pregnancy prevalence of 2.4% with a rise to 14.3% in adolescent women and a report from the USA suggested an even higher prevalence in pregnant adolescents (18%).<sup>46,47</sup> This is certainly a source of great concern as it appears that *C. trachomatis* is relatively efficiently transferred from infected mother to neonate during vaginal delivery. The risk for neonatal acquired conjunctivitis is in the region of 15–50% and for neonatal acquired chlamydial pneumonia somewhere between 5% and 30% depending upon the test used for *C. trachomatis* detection.<sup>48–52</sup> Furthermore, it is likely that asymptomatic neonatal transmission from infected mothers is even higher, in the region of 50–70% if nasopharyngeal and serological specimens are both included for analysis.<sup>52</sup> It is true that vaginal delivery poses the greatest risk of neonatal transmission though there are rare case reports of neonatal infection following caesarean section, both with and without prior membrane rupture.<sup>53</sup> Although the efficiency of sexual transmission of *C. trachomatis* from partner to partner is unknown, it is likely to be higher from male to female than in reverse. One estimate derived from contact tracing studies

**Table 40.1:** Estimated New Cases of *Chlamydia trachomatis* Infections (in Millions) Among Adults, 1995 and 1999

Region	1995			1999		
	Male	Female	Total	Male	Female	Total
North America	1.64	2.34	3.99	1.77	2.16	3.93
Western Europe	2.30	3.20	5.50	2.28	2.94	5.22
North Africa & Middle Europe	1.67	1.28	2.95	1.71	1.44	3.15
Eastern Europe & Central Asia	2.15	2.92	5.07	2.72	3.25	5.97
Sub-Saharan Africa	6.96	8.44	15.40	7.65	8.24	15.89
South and Southeast Asia	20.20	20.28	40.48	18.93	23.96	42.89
East Asia & Pacific	2.70	2.63	5.33	2.56	2.74	5.30
Australia & New Zealand	0.12	0.17	0.30	0.14	0.17	0.30
Latin America & Caribbean	5.01	5.12	10.13	4.19	5.12	9.31
Total	42.77	46.38	89.15	41.95	50.03	91.98

confirms infection rates of 65% for female partners of men with chlamydial urethritis.<sup>54</sup>

Chlamydial infection is also common outside the developed world. Globally in 1999 it is estimated that approximately 92 million cases occurred, affecting 52 million women and 40 million men. Statistics gathered and published by the World Health Organization (WHO) shows that rates of infection appear to have fallen over recent years in some regions while rising in others (See Table 40.1).<sup>55</sup>

## C. trachomatis and HIV Transmission

There has been some speculation regarding the role of *C. trachomatis* in enhancing HIV acquisition and a number of prospective cohort studies do suggest an association. A small study from Thailand found an adjusted risk ratio of 3.3 for cervical chlamydial infection and HIV seroconversion and a larger study in Zaire of 430 HIV-negative female sex workers showed an odds ratio for HIV seroconversion among those with chlamydial infection of 3.6.<sup>56,57</sup> It seems scientifically plausible that *C. trachomatis* infection of genital sites could recruit greater numbers of immune and inflammatory cells which would then act as ready targets for any HIV organisms present.

## Pathology

Intracellular inclusion bodies are the hallmark of infection with *C. trachomatis*. They were first described in trachoma in 1907 and subsequently in cells within urethral discharge.<sup>58</sup> Similar findings have been noted in histological sections of cervical mucosa

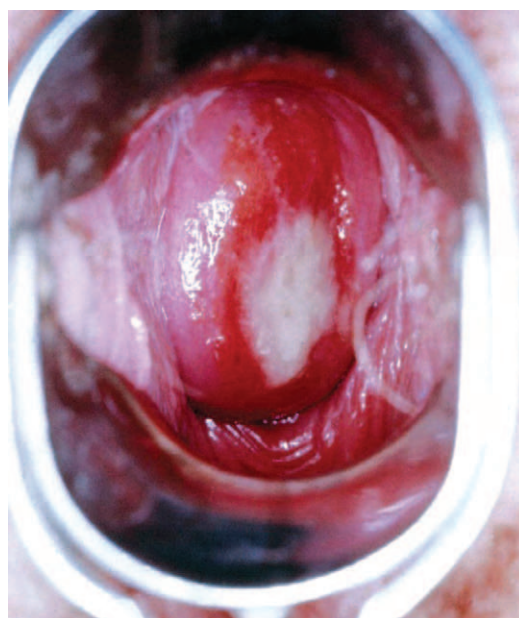
infected with the organism.<sup>59</sup> Rectal infection with the *trachoma biovar* may correspondingly produce little in the way of visible pathology though there may be the appearance of a nonspecific proctitis with an inflammatory infiltrate.<sup>60</sup> Inclusion bodies are cytoplasmic vacuoles readily seen on light microscopy and when examined in more detail using electron microscopy can be seen to contain many small spherical organisms which are the EB of *C. trachomatis*. Infection with LGV serovars produces a very different pathological picture with a local lymphoproliferative response and the development of true lymphoid follicles within the mucous membranes.<sup>61,62</sup>

The immune response to chlamydial infection is also evident pathologically. In the *trachoma biovar* neutrophil polymorph cells are seen in abundance and there is also an infiltration of macrophages, T and B lymphocytes.<sup>63</sup> It is this inflammatory response that probably results in the scarring of mucous membranes often seen following chlamydial infection. Certainly reinfection with *C. trachomatis* appears to result in more severe disease in primates and humans and is associated with a higher rate of complications.<sup>64,65</sup> It has been postulated that the chlamydial heat shock protein (HSP60) may be the target of the inflammatory response, hypersensitivity to which results in the cellular destruction often seen following infection with this organism.<sup>66,67</sup>

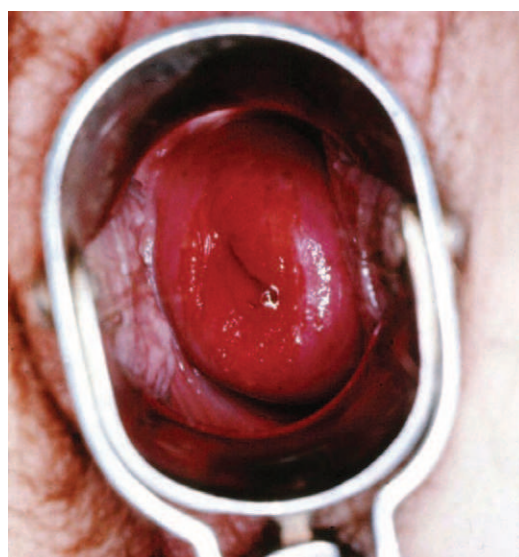
## Clinical Features

A significant proportion of infections with *C. trachomatis* produce no discernible symptoms in the host, thereby facilitating transmission of the pathogen to others.<sup>2,68</sup> This is particularly true in women, where cervical infection is the most common site affected. In such cases women may have an asymptomatic cervicitis (Fig. 40.4a,b), visible only on clinical examination, or may complain of such symptoms as increased vaginal discharge, post-coital/intermenstrual bleeding or lower abdominal pain.<sup>69,70</sup> Clinical signs of chlamydial infection in women also vary accordingly and physical examination may reveal no abnormality of the cervix, or in some cases mucopurulent discharge associated with cervical friability. Women with *C. trachomatis* may also present with symptoms or signs related to urethral infection, namely urinary frequency, dysuria, or suprapubic pain.<sup>71</sup> Urethral swabbing or urinalysis will confirm pyuria but no organisms will be demonstrated on gram stain or culture.

In men, chlamydial infection can also be harbored without symptoms, however, *C. trachomatis* is the most commonly identified cause of NGU and therefore may present with symptoms such as dysuria and/or urethral discharge (Fig. 40.5).<sup>1,72</sup> As in the case of urethral infection in women, urethritis can be confirmed by the presence of leukocytes on a gram-stained urethral smear prior to specific tests to identify *C. trachomatis*. In some patients an erosive or papular, painless rash may be found on the penis in association with chlamydial infection and this is described as circinate balanitis (Fig. 40.5).<sup>73</sup>



\*c+



\*d+

**Fig. 40.4:** Chlamydial infection of the cervix: mucopurulent cervicitis (a) before treatment, and (b) 6 weeks after treatment with tetracycline. Courtesy: E Rees: From: Arya OP and Hart CA, eds. Sexually Transmitted Infections and AIDS in the Tropics. CAB International, Wallingford, Oxon, 1998, Plates 98 [a] and [b].

*Chlamydia trachomatis* may infect the rectum in both sexes, although actual symptomatic proctitis is rare with the non-LGV serovars.<sup>74</sup> Occasionally men who have sex with men (MSM) may present with a distal proctitis secondary to *C. trachomatis*, the most common symptoms of which are anorectal pain, rectal discharge, and/or tenesmus.<sup>7,75</sup> Symptomatic proctitis is much more commonly seen with LGV. Chlamydial conjunctivitis can





**Fig. 40.5:** Penile discharge and circinate balanitis in association with urethral *Chlamydia trachomatis* infection.



**Fig. 40.6:** Conjunctivitis caused by *Chlamydia trachomatis*.

also occur in both sexes, most commonly in association with concurrent genital infection (Fig. 40.6).<sup>76</sup>

In an infected neonate the most common clinical presentation is conjunctivitis presenting up to 2 weeks after delivery. The conjunctivitis may be mild to severe ranging from a watery discharge to a blood-stained mucopurulent exudate and although early treatment favors an excellent prognosis, untreated infection can cause scarring.<sup>77,78</sup> Neonates infected during delivery with *C. trachomatis* may less commonly present with pneumonia, evident within 2 to 8 weeks after birth in the majority of cases. This is usually manifested as a cough accompanied by tachypnea with variable hypoxemia and bilateral interstitial infiltrates on a chest radiograph.<sup>79</sup>

LGV has a clinical presentation classically consisting of three phases.<sup>80</sup> The primary lesion appears 3–30 days after infection but is transient and can be missed. It may be a painless papule or pustule or shallow erosion, usually found on the coronal sulcus

in men and on the posterior vaginal wall fourchette or vulva in women. Cervical and extragenital lesions have been reported such as in the oral cavity and extragenital lymph nodes.<sup>81,82</sup>

The secondary stage of LGV is characterized by inflammation and swelling of lymph nodes and surrounding tissue with large necrotic lymph node (bubo) formation. This is usually inguinal or femoral in location, frequently unilateral and may involve a single or many nodes. Nodes may progress to ulceration and discharge pus from multiple points, creating chronic fistulae. The majority of patients with LGV infection recover after the secondary stage without sequelae, but in a few patients progressive spread of *C. trachomatis* incites a chronic inflammatory response including proctitis, acute proctocolitis mimicking Crohn disease, fistulae, strictures, and a chronic granulomatous disfiguring condition of the vulva.

In the recent outbreaks occurring among MSM in Western Europe and the USA almost all cases of LGV presented with proctitis. Symptoms included severe rectal pain, mucous and/or hemorrhagic rectal discharge, tenesmus, constipation, and other signs of lower gastrointestinal inflammation, often severe. In these more recent cases, genital ulcers and inguinal symptoms appear to be rare manifestations of LGV.<sup>83</sup>

## Complications

Untreated *C. trachomatis* infection in women will lead to pelvic inflammatory disease in 10–40% of cases, although a proportion of these will be asymptomatic.<sup>5,84,85</sup> Patients with pelvic inflammatory disease may present with pelvic pain, fever, and systemic upset or dyspareunia, and symptomatic or asymptomatic infections may later present with tubal factor infertility, chronic pelvic pain or ectopic pregnancy.<sup>86,87</sup>

In men *C. trachomatis* infection may lead to epididymo-orchitis with pain, erythema, and swelling of the scrotal contents.<sup>88</sup> In contrast with women, however, chlamydial infection has not been proven to cause infertility in males.<sup>89</sup>

A small percentage of men with urethral chlamydial infection will develop a reactive arthritis and of these, up to a third will manifest the triad known as Reiter syndrome, i.e., arthritis, urethritis, and conjunctivitis.<sup>73,90</sup> Although advances in molecular diagnostic testing for *C. trachomatis* have enabled the identification of chlamydial DNA in synovial tissue in some such cases it is not universally present.<sup>91,92</sup> Similarly, treatment of such patients with longer courses of antibiotics does not appear to alter the likelihood of, or time to, resolution of joint symptoms.<sup>93</sup>

Occasionally *C. trachomatis* infection can cause perihepatitis with inflammation of the liver capsule and this is more common in the context of pelvic inflammatory disease.<sup>94</sup> In such cases, referred to as Fitz-Hugh-Curtis syndrome, the patient will complain of right upper quadrant pain, worse on inspiration although liver enzyme analysis is usually normal. The exact mechanism of the perihepatitis is uncertain and it may result from either direct infection spread through the peritoneum or by immune-mediated means.

Long-term complications of untreated LGV can include lymph node destruction with resulting lymphedema of the genitals (elephantiasis) and persistent suppuration.<sup>80,95</sup>

## Diagnosis

*C. trachomatis* cannot be cultured on artificial media and therefore traditionally tissue culture was used to establish a diagnosis. Recent advances in molecular diagnostic technology however have revolutionized the diagnosis of *C. trachomatis* infection. Although available diagnostic tests for *C. trachomatis* still include culture, enzyme-linked immunosorbent assay (ELISA) and direct immunofluorescence (DIF), the most sensitive and specific tests are now based on nucleic acid amplification techniques (NAATs).<sup>96–98</sup> These include polymerase chain reaction (PCR), transcription mediated amplification (TMA), and strand displacement amplification (SDA) tests, and have the advantage of being able to be performed on urine samples as well as genital swabs.<sup>99</sup> The sensitivities of NAATs in cervical and urethral swabs are more than 95% and although these tests have been validated in urine samples for both men and women more variable sensitivities have been reported using urine in women.<sup>100–103</sup> More recently however, in female patients self-taken vulvovaginal swabs have been demonstrated to have similar sensitivities to a physician-taken cervical swab.<sup>100,104</sup>

When obtaining samples for *C. trachomatis* testing from extra-genital sites (rectal, pharyngeal, and conjunctival), it should be noted that currently no NAATs have licensing approval for these sites. Despite this, in the absence of culture or DIF many clinical centers in the UK and elsewhere are using NAAT tests for samples from these sites with consistently reproducible results.

The one current disadvantage of NAAT based tests for *C. trachomatis* concerns the time taken to receive a test result, usually some days. For this reason some 'point of care' or 'rapid chlamydia tests' have been piloted. These immunoassay-based procedures are based on monoclonal antibody binding to chlamydial antigens from self-taken vaginal swabs and can provide results within 30 minutes of specimen taking with the additional advantage of being cheaper than NAAT tests and uncomplicated to interpret.<sup>105</sup> This type of test has obvious potential uses in resource-limited settings, however sensitivity results to date have been disappointingly variable precluding their more widespread use at present.<sup>106,107</sup>

Serological testing is generally not helpful in the diagnosis of genital tract *C. trachomatis* infection since the presence of antibody may simply be a reflection of past infection with the organism or cross reaction with *Chlamydothila pneumoniae*. Although seroconversion from negative to positive or alternatively a fourfold rise in titer may correlate with the isolation of *C. trachomatis* this is rarely clinically useful as the antibodies may take in excess of 4 weeks to be detectable.<sup>108</sup>

## Treatment

Uncomplicated cases of genital chlamydial infection can be treated using a single 1 g dose of azithromycin given orally. An alternative appropriate treatment is doxycycline 100 mg twice daily orally for 7 days. Both of these antibiotic options have been extensively used and demonstrate a similar high cure rate of >95% at follow-up.<sup>109,110</sup> Second-line treatments for *C. trachomatis* include erythromycin (500 mg twice daily for 10–14 days) and ofloxacin (200 mg twice daily or 400 mg once daily for 7 days). Ofloxacin has comparable efficacy to doxycycline; however, it has been suggested by a number of studies that erythromycin may be less effective, particularly if given for less than 10 days.<sup>110–112</sup>

When infection with *C. trachomatis* is found during pregnancy, a number of treatment options may be considered. Erythromycin 500 mg 4 times daily for 7 days can be given but may be poorly tolerated because of side-effects.<sup>113</sup> There are, however, no trial data to confirm efficacy of the better tolerated regimen of erythromycin 500 mg twice daily for 14 days. Azithromycin 1 g single dose is not currently licensed for use in pregnancy; however, many clinicians are happy to prescribe it, and available data suggest that it is safe to do so.<sup>114</sup> Where erythromycin is not tolerated and there is a wish to avoid azithromycin then amoxicillin 500 mg 3 times daily for 7 days can be used.

Uncomplicated rectal infection with non-LGV chlamydial strains may be treated with azithromycin 1 g orally, however the cure rate may be less than 90%.<sup>115</sup> LGV infection is more invasive and therefore requires a longer period of systemic treatment for eradication. In confirmed cases it is suggested to give 21 days of doxycycline at a dose of 100 mg twice a day or an alternative regimen is 21 days of erythromycin 500 mg 4 times daily.<sup>116</sup>

## Vaccines

Although several *C. trachomatis* antigens have been suggested as potential vaccine candidates, attempts to produce a prophylactic vaccine have not been successful to date.

Early attempts in the 1960–70s used whole, killed *C. trachomatis* and initially short-term protection seemed to be produced in experimentally infected blind volunteers. Subsequently however, vaccination appeared to enhance the severity of ocular disease in individuals reinfected with the organism hence such efforts were abandoned.<sup>117</sup>

The ability of *C. trachomatis* to cause repeated infections in the same host suggests that a vaccine induced immune response would need to be greater than the natural immune response in the host. In addition the situation is complicated by the fact that correlates of natural immunity to *C. trachomatis* in humans are not yet fully understood.<sup>118</sup> Animal studies and observational cohort studies in humans with human immunodeficiency virus (HIV) infection suggest that CD4+ T-lymphocytes may play an important role, particularly those which are T-helper Type 1 MOMP-specific,

however the role of the CD8+ T-cell appears less clear.<sup>119–123</sup> This is thought to be in part a result of the intracellular, membrane-protected lifecycle of the *C. trachomatis* organism which largely prevents its degradation and presentation to CD8+ cells. Despite this, antigen-specific CD8+ cytotoxic T-cell responses have been demonstrated in the setting of chlamydial infection.<sup>124,125</sup> The role of antibodies in immunity to *C. trachomatis* infection seems similarly complex. Although serum antibody titers do not correlate with protection it appears that local IgA mucosal protection may play a more important role.<sup>126–129</sup>

Vaccine studies to date suggest that a successful candidate vaccine would need to induce CD4+ T-Helper Type 1 responses (via interferon-gamma) and also a humoral response to be effective. Recent efforts have been focused on recombinant MOMP vaccines which avoid the potential safety concerns which can be associated with live attenuated or killed, whole-organism products.<sup>130</sup> Recombinant MOMP it seems, however, is not easy to produce, particularly on a large enough scale for commercial vaccination purposes. Research groups therefore continue to investigate novel protective antigens and delivery systems which will hopefully yield more promising and durable results.<sup>119,131–134</sup> In particular *C. trachomatis* DNA vaccines appear to be promising candidates and are undergoing analysis by several major vaccine companies.<sup>135–138</sup>

## Prevention

Prevention of sexually transmitted infections such as *C. trachomatis* necessitate a multi-faceted approach including public education, the treatment of known infected individuals, the screening and treatment of their contacts, and screening of asymptomatic individuals who may carry the organism and be capable of transmitting it.<sup>139</sup>

The prevalence of asymptomatic untreated chlamydial infection is high as illustrated in cross-sectional studies from the UK which suggest estimates of 10–13% and are likely to be even higher in the developing world.<sup>140</sup> Screening of those who may be asymptotically infected ideally needs to be targeted towards those at risk and a number of risk factors for chlamydial infection have been identified to date. These include age (adolescents and young adults), recent change in sexual partner, a high number of lifetime sexual partners, non-use of barrier contraceptives, a history of previous sexually transmitted disease, and lower educational or socioeconomic status.<sup>140–145</sup> In addition, screening requires a minimally-invasive, sensitive, and specific test which is applicable across large population groups. Again the advances in NAAT testing for detection of *C. trachomatis* have facilitated the development of potential screening programs, though their relatively high cost may preclude their widespread use in resource-poor settings.<sup>96,146</sup> Finally, the relative ease with which *C. trachomatis* can be treated also contributes to its consideration as a target of a

primary prevention screening program, as does the potential likelihood of complications from untreated infection. In a randomized controlled trial screening women at risk of chlamydial infection was associated with a reduced rate of pelvic inflammatory disease.<sup>147</sup>

Sweden was the first country to commence a screening program for asymptomatic chlamydial infection which began in 1982.<sup>148</sup> This opportunistic approach targeted women less than 30 years of age who presented seeking contraception, termination of pregnancy, or antenatal care. Initially rates of *C. trachomatis* fell in the 1990s and this was cited as evidence of success of the screening program. However, it should be noted that decreases in the rate of chlamydial infection in Sweden also corresponded with the national HIV awareness campaign and paralleled decreases in other countries where a *C. trachomatis* screening program was not in operation.<sup>149</sup> In keeping with this, rates of *C. trachomatis* infection in Sweden have risen again since 1995 thus effectiveness of the screening program has yet to be conclusively proven.<sup>150,151</sup> In the USA the Centres for Disease Control (CDC) have supported chlamydial screening since 1988 asserting that all pregnant women be screened at the first antenatal visit with repeated testing in the third trimester in those who are 24 years or younger, or at increased risk in order to reduce neonatal chlamydial infection.<sup>152</sup> In addition the CDC recommends the annual screening of all sexually active women under 26 years of age or those with risk factors for chlamydial infection. In the USA it has been decided that there is insufficient evidence to recommend routine screening of all men but targeted male populations such as those attending sexually transmitted infection clinics and those in prison should be screened for *C. trachomatis*. As in Sweden, chlamydia screening in the USA is voluntary; hence overall adherence to the USA recommendations appears to be poor with uptake of screening by only 26–38% of potentially eligible women.<sup>153</sup>

In the UK the National Chlamydia Screening Programme (NCSP) has been established in England, offering opportunistic *C. trachomatis* screening to all sexually active men and women less than 25 years old in a variety of healthcare and educational settings.<sup>140,154</sup> This program has unfortunately suffered from the same problems as the USA, with poor uptake in many areas despite a co-ordinated and extensively funded national approach. In 2008–2009, when the national rollout of the program was completed, the target for *C. trachomatis* testing among 15–24 year olds was set at 17%. The figure reached was only 15.9%, and with the 2009/10 target raised to 25% it seems unlikely that this will be achieved.<sup>155</sup>

Theoretically *C. trachomatis* remains a candidate for screening programs though there appears to be a lack of evidence of effectiveness of such programs at present. The mode and frequency of screening, as well as the target populations and cost-benefit ratios in areas with varying prevalence of infection are all still subjects of much debate.



## Summary

*Chlamydia trachomatis* is the most common bacterial sexually transmitted infection in the world today with in excess of 90 million cases reported annually worldwide. Infection is commonest in younger men and women and is also associated with a high number of sexual partners and low educational/socioeconomic status. It exists as an obligate intracellular bacterium with two distinct forms—the elementary body (which is the infectious form) and the reticulate body (which is the metabolically active form). *C. trachomatis* is classified into several distinct serovars that are responsible for specific clinical syndromes including tropical trachoma (*C. trachomatis* biovar *trachoma* serovars A-C), genital tract infections (*C. trachomatis* biovar *trachoma* serovars D-K), and proctitis/lymphadenitis (*C. trachomatis* biovar *lymphogranuloma venereum* [LGV] serovars L1-L3).

A significant number of infections with *C. trachomatis* produce no symptoms in the host. Alternatively women may present with pelvic pain, irregular vaginal bleeding or discharge, and men with symptoms of urethritis, namely dysuria and urethral discharge. Chlamydial proctitis may also be asymptomatic, although LGV infection tends to produce rectal pain, discharge or bleeding in the host. Complications of *C. trachomatis* infections include pelvic inflammatory disease, epididymo-orchitis, Reiter syndrome, and female infertility. In current times, *C. trachomatis* is most frequently diagnosed using nucleic acid amplification tests (NAATs), although tissue culture can still be used. NAATs are not currently licensed for use on samples from extra-genital sites, but are widely used with good clinical reproducibility.

Treatment of uncomplicated *C. trachomatis* infection can be in the form of a single 1 g oral dose of azithromycin or a week's course (100 mg twice a day) of doxycycline, both of which have a cure rate of >95%. Erythromycin can be used in pregnancy or in the penicillin-sensitive patient. LGV requires a longer treatment course of doxycycline (100 mg twice a day for 21 days).

Globally, several screening programs exist for the detection of *C. trachomatis* in patients thought to be at risk including those in Sweden, USA, and the UK. In all cases, screening is opportunistic, mainly directed at women and suffers from less than ideal uptake. Although there have been several proposed *C. trachomatis* antigens as vaccine candidates, none have been successful to date and work continues in this area.

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# Lymphogranuloma Venereum

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## Introduction

Lymphogranuloma venereum (LGV) is a sexually transmitted chlamydial disease that primarily involves the lymphatics. Many synonyms have been used in the past for this condition, such as tropical bubo, climatic bubo, paradenitis inguinalis, Durand–Nicolas–Favre disease, lymphopathia venereum, and the fourth, fifth or sixth diseases. However, the name LGV is prevalent because it clearly differentiates it from another sexually transmitted disease, granuloma inguinale. The disease is universal in occurrence with a large number of cases seen in the tropical parts of Africa, Asia, and South America. Since 2003 it is endemic among men who have sex with men (MSM) with high risk sexual behavior, especially in Europe but it is also found in North America and Oceania. Recently several endemically transmitted heterosexual cases of LGV have been reported from Spain and Portugal. The etiologic agent is *Chlamydia trachomatis* biovars L-1, 2, 3. The nomenclature to identify different *C. trachomatis* strains depends on the diagnostic method used. For antibody based techniques the term serovar is used, and for nucleic acid based tests the term biovar. For the sake of clarity the more general term biovar is used throughout this chapter.

## History

LGV is an ancient disease, known since the 18th century, and the historical aspects of this disease have been extensively reviewed in the monographs by Stannus, Kampmeier et al., Koteen, Favre and, Hellerstrom, and Rajam and Rangiah. Though the initial description of LGV was attributed to Wallace (1833),<sup>1</sup> the venereal nature of this condition was pointed out by Nelaton (1890) and his pupil, L'Hardy (1894). In India, Caddy was the first to describe this condition in 1902 under the name “climatic bubo.” LGV was often confused with the lymphadenopathy of other diseases, such as tuberculosis, syphilis, and chancroid. Durand, Nicolas and Favre for the first time established it as a distinct clinico-pathologic entity in 1913 under the name “lymphogranuloma inguinale” In 1922, Phylactos suggested a common etiology of climatic bubo and LGV.

One of the significant milestones in the diagnosis of LGV was the development of an intradermal test by Frei in 1925 by using aspirated pus from the unruptured bubo as antigen. Viral etiology of this condition was suspected by Hellerstrom et al.<sup>2</sup> The organism was isolated successfully by Favre et al. in 1930 after intracerebral inoculation of monkeys with the aspirate obtained from buboes.<sup>3</sup> In 1935, Miyagawa succeeded in growing the LGV related *Chlamydia* in embryonated hen's eggs and made possible the production of large amounts of antigen for the Frei test and other serodiagnostic investigations. A complement fixation test was developed in 1930.<sup>4</sup> Sheldon and Heyman in 1947 described the histopathologic features of LGV by observing the pathognomic “stellate abscesses” in the affected lymph nodes.<sup>5</sup> Recent developments in the diagnosis of LGV include the introduction of biovar specific nucleic acid amplification tests (NAATs) which are generally considered the gold standard in LGV diagnostics.<sup>6,7</sup> Older techniques which are used less frequently today are the micro-immunofluorescent test by Wang et al.,<sup>8</sup> introduced in 1975, culture of the organism and other cytologic methods of detection.<sup>9,10</sup>

## Epidemiology

LGV was formerly known as a sexually transmitted infection confined to equatorial regions but also as an “imported” sexually transmissible infection in the Western world. However since 2003, with the first cases of LGV proctitis among MSM reported in the Netherlands, an ongoing epidemic has been revealed in Western society dating back to at least 1981.<sup>11–14</sup>

In the beginning of this MSM associated LGV epidemic the great majority of cases were caused by biovar L2b, also known as the Amsterdam variant, and confined to a “core group” of HIV positive individuals with multiple co-infections like hepatitis C, engaging in high risk sexual behavior like unprotected anal intercourse, multiple anonymous partners, group sex, and use of anal enemas.<sup>15–17</sup> Recently there are reports from Spain and Portugal of heterosexual spread of LGV infections caused by the L2 biovar, but not the specific L2b biovar which causes most LGV infections among MSM in

Europe.<sup>18,19</sup> Nonetheless, it is feasible that the MSM LGV epidemic has spread from the initial “core group” via a bridging population to the community at large. An excellent review of the recent LGV epidemic among MSM has been written by White.<sup>20</sup>

Until 1990s, LGV was endemic in several tropical and subtropical countries including West, Central and East Africa, India, Malaysia, Korea, Vietnam, South America, Papua New Guinea, and the Caribbean Islands.<sup>21–26</sup> Perhaps, the lack of specific diagnostic criteria in these studies and the relatively poor degree of clinical suspicion of this condition may have biased these estimates. Two cross-sectional surveys undertaken in STD clinics in Jamaica in 1982–83 and 1990–91 revealed disease prevalence of 4.1% and 3.9%, respectively. In 1996, the prevalence decreased to 2.63%.<sup>27</sup> An epidemic of LGV has been reported from the Bahamas and it was attributed to epidemics of crack cocaine use and HIV infection.<sup>28</sup> In Madagascar in 1997, 8% of genital ulcer disease patients were clinically diagnosed as LGV with only 0.5% accounting for confirmed cases by micro-IF test.<sup>29</sup> In Hong Kong, the disease accounted for only 0.001% of all the new STD cases in 1995.<sup>30</sup> A prevalence of 1% was recorded in STD clinics in Singapore in 1995.<sup>31</sup> In Nairobi, Kenya, 0.6% of genital ulcer disease was attributed to LGV in 1996.<sup>21</sup> In South Africa, LGV was seen in 3.2–11% of patients with genital ulcer disease.<sup>32,33</sup> In Nigeria, LGV was the most common cause of genital ulcers in women attending STD clinics.<sup>34</sup> A prospective study of inguinal buboes conducted in Thai men between 1987 and 1989 revealed LGV-*C. trachomatis* by immunofluorescent microscopy in 3.9% of the cases.<sup>25</sup>

However, late reports suggest that the disease has declined considerably in tropics and only sporadic cases are reported. In an STD clinic in New Delhi, India, LGV comprised of 3.4% of all STD cases (5.7% in males and 0.3% in females) during 1990–1993, in comparison to only 0.2% during 2002–2004 (0.4% in males and 0% in females).<sup>35</sup>

LGV has been reported to occur more frequently in men than in women. It probably remains underdiagnosed because of the asymptomatic nature of the early lesions in women.<sup>36</sup> However, in a more recent study performed in Durban, South Africa, among 520 consecutive consenting patients presenting with genito-ulcerative disease between October 2000 and April 2001, the prevalence of LGV in women was 19% versus 10% in men ( $P = 0.006$ ).<sup>37</sup> Late complications, such as ulceration, rectal strictures, or esthiomene, are more frequently reported in women. The disease has a peak incidence during the second and third decades of life which corresponds with the peak age of sexual activity. It is more common in urban populations, among MSM in Western society, among the sexually promiscuous and lower socio-economic classes. To date, the specific LGV epidemic among MSM presenting with acute proctitis has not been identified other than in Western countries.<sup>38</sup> Commercial sex workers play a major role in disease transmission, as was documented during an outbreak in Florida in the late 1980s.

Sexual intercourse is the most common mode of disease transmission. Primary LGV lesions of the mouth and pharynx

occur as a result of receptive oral sex.<sup>39</sup> However, non-venereal transmission to healthcare personnel from ruptured buboes and other infected tissues has also been reported. There are reports of laboratory acquired infection following inhalation of highly concentrated virulent culture material.<sup>40</sup> Transplacental transmission has not been documented, although the infection may be acquired through an infected birth canal.<sup>41</sup>

## Biology

LGV is caused by *Chlamydia trachomatis* biovars L1, L2, and L3, of which L2 is the most common serotype. By the end of the last century, the rarer L1 biovar had been identified in MSM with proctitis.<sup>42</sup> In the recent epidemic among MSM a new variant L2b (also known as the Amsterdam variant) has been identified which has been circulating unnoticed for decades in the United States and Europe until the outbreak was unveiled in 2004.<sup>43</sup> The clinical manifestations of this strain are less severe than the L2 biovar.

Chlamydiae are a group of intracellular microorganisms causing pneumonia, psittacosis, trachoma and LGV in humans, and diverse diseases in many avian and mammalian species. They are filterable organisms, do not grow in cell free media, possess a cell wall, multiply by binary fission, contain both DNA and RNA and are obligate anaerobes that do not contain a cytochrome system or produce ATP.<sup>44</sup> This genus is classified into two species. *Chlamydia psittaci*, a common pathogen of avian and mammalian species, forms diffuse vacuolated inclusions without a glycogen matrix and is resistant to sulfonamides. *Chlamydia trachomatis*, a natural human parasite, causes infection of the eye and genitalia. It forms compact inclusion bodies, contains glycogen matrix and is sensitive to sulfonamides.<sup>45</sup> *Chlamydia trachomatis* contains three biovars, that is, murine, LGV, and trachoma biovars.<sup>46</sup> They are classified into 15 biovars on the basis of neutralization and immunofluorescent tests, of which A, B, Ba, and C cause endemic trachoma, types D to K cause oculo-genital infection, and biovars L1, L2 and L3 are responsible for LGV. There is almost complete DNA homology between LGV and trachoma biovars. They are also related serologically but differ in the type of cells they invade. The trachoma biovar infects only squamo-columnar cells, whereas LGV strains are more invasive and penetrate and replicate within macrophages. They are lymphotropic organisms that cause thrombolympangitis and perilymphangitis.<sup>47</sup> Recently, Thomson et al. completed the genomic analysis of the remaining *C. trachomatis* biovariant, LGV.<sup>48</sup> They found that the LGV genome is remarkably similar to the previously sequenced ocular and genital *C. trachomatis* isolates. This rules out the possibility that additional acquired DNA present in *C. trachomatis* strain L2 could explain differences in tissue tropism and disease outcome. Gene loss and/or small-scale mutational change are the major driving forces determining host adaptation and tissue tropism of different biovars of *C. trachomatis*.

Trachoma and LGV biovars differ in their heparin-inhibitable interaction with mammalian cells. Serovar L1 is significantly



more dependent on a heparan sulfate-related mechanism of infectivity than is serovar E. In LGV biovars a 60 kDa OmcB protein has been reported to bind heparan sulfate.<sup>49</sup> It is thought that OmcB might be responsible for the differences in the clinical presentations of trachoma biovars and LGV biovars.<sup>50</sup>

## MORPHOLOGY

Chlamydiae are complex microorganisms that were earlier considered to occupy a position intermediate between bacteria and viruses. Following the suggestion of Moulder, they are considered as small bacteria adapted to obligate intracellular parasitism.<sup>51</sup> The LGV-*Chlamydia* elementary body (EB) consists of an outer cell wall, which is made up of geometrically arranged, 20 nm diameter subunits, that lack the muramic acid and peptidoglycan moiety.<sup>52</sup> The cell wall possesses two types of antigen; a common heat stable, complement fixing antigen that can be extracted in either deoxycholate, chloroform or methanol, and a type specific, heat-labile antigen, which is extractable with trypsin or deoxycholate and helps differentiate the different biovars by complement fixation or neutralization tests. It produces an endotoxin like factor, which is responsible for constitutional symptoms of fever, chills, and fatigue that precede the onset of inguinal LGV. Like all Gram negative bacteria, lipopolysaccharide is a surface component of *C. trachomatis*.

Inner to the cell wall is the trilaminar outer membrane that contains a 38–43 kDa, cysteine-rich major outer membrane protein (MOMP).<sup>53</sup> This protein shows disulfide linkage and maintains the structural and functional integrity of the outer membrane. A reduction in disulfide linkage occurs when the elementary body (EB) changes to reticulate body (RB). MOMP is a porin that plays an important role in the attachment of EBs to host cells. Nine polymorphic MOMP genes (pmp A to pmp H) have been identified in the genome of biovar L2.<sup>54</sup> The L1 biovar MOMP contains 371 amino acids while L2 contains 372 amino acids. Other proteins that are detected in the outer membrane include polymorphic OMPs E, G, and H, a mixture of 46 kDa proteins, modified forms of MOMP, penicillin binding proteins and Mip-like protein.<sup>55</sup> The Mip-like protein is a 27 kDa protein with homology of the 175-amino acid C-terminal fragment to the surface exposed *Legionella pneumophila* Mip-gene product.

Inner to the outer membrane is the inner membrane and periplasmic space. The organism possesses both DNA and RNA. However, there is no detectable thymidine kinase and DNA synthesis occurs via the uridine and thymidylate synthetase pathway.<sup>56</sup> There is also present a 4.4 MDa plasmid and the genome contains 16S RNA genes.<sup>57,58</sup>

Several mechanisms by which *Chlamydia trachomatis* attaches to and infects host cells have been described. Proposed ligands include the major outer-membrane protein (MOMP), heat-shock protein 70 and glycosaminoglycans. A cryptic 7.5 kb plasmid of unknown function is maintained by human Chlamydial strains. This is associated with accumulation of glycogen, while the plasmid-less isolates fail to do so. Carlson et al. demonstrated in

LGV biovars that the plasmid's biological effect on chlamydial pathogenesis is associated with *in vivo* infection, which enhances the pathogen's ability to colonize and sustain infection in the mouse female genital tract.<sup>59</sup> Fedel and Eley's work suggests that *C. trachomatis* lipopolysaccharide plays a role in infectivity towards epithelial cells. They demonstrated that *C. trachomatis* LPS and *C. trachomatis* LPS antibody significantly reduced infectivity, mostly in a dose-dependent manner. However, with all the LPS inhibitors used, there was greater inhibition against biovar E than biovar LGV1.<sup>60</sup>

## STAINING PROPERTIES

The EB is gram-negative but stains readily with Giemsa, Castaneda, Machiavello, or Gimenez stains. It stains faint blue with hematoxylin and eosin, and black with Warthin–Starry silver impregnation stain. The RB is basophilic and can be stained with Lugol's iodine due to the presence of glycogen matrix. The organism is Periodic acid-Schiff (PAS) negative and not acid-fast.<sup>61</sup>

## RESISTANCE

The organism is heat-labile, being inactivated within minutes at 56°C. It is susceptible to ethanol, ether, and low concentration of phenol and formalin. Infectivity is maintained for several days at 4°C and indefinitely at -70°C.<sup>62</sup>

## GROWTH PROPERTIES

LGV-*Chlamydia* can be propagated in the yolk sac of developing chick embryos, HeLa cells, mouse, and tissue cultures.<sup>63</sup> It forms plaques in cell culture. Unlike the trachoma biovar, infectivity of the host cells is not enhanced by centrifugation or pretreatment with DEAE dextran.<sup>64</sup> Addition of exogenous heparin or heparin sulfate *in vitro* inhibits the infectivity and attachment of the LGV biovar to host cells suggesting that it uses predominantly a heparin-inhibitable mechanism.<sup>65</sup> Growth can be regulated by the addition of essential amino acids derived from either the host cell nutrient pool or from degradation of host proteins. Cysteine is a major amino acid in the OMP and is essential for the differentiation of EB from RB.<sup>66</sup> Cyclic-AMP inhibits chlamydial growth by inhibiting this transformation.<sup>67</sup> Estradiol enhances the growth by lowering cAMP levels.<sup>68</sup>

## Pathology

The causative agent of LGV is a lymphotropic organism that initiates the disease process by causing thrombolympangitis and perilympangitis.<sup>41</sup> After inoculation through abraded skin or mucous membrane, the organisms become concentrated in draining lymph nodes and produce lymphangitis and lymphadenitis. They stimulate endothelial cell proliferation in the lymphatic vessels and lymph channels within lymph nodes. The regional lymph nodes enlarge and undergo necrosis. This is followed by neutrophilic chemotaxis

leading to formation of triangular or quadrangular “stellate” abscesses that become surrounded by epithelioid cells, macrophages and giant cells. These abscesses coalesce to form a multiloculated abscess, which ruptures spontaneously resulting in fistulae and sinus tracts. The inflammatory process subsides with fibrosis, which obstructs the subcutaneous and submucous lymphatic channels resulting in lymphedema, brawny induration of the affected part, and elephantiasis. The regional blood supply is compromised secondarily, which causes ischemic necrosis and ulceration of the overlying skin and mucous membrane. This sequence of events is responsible for “esthiomene” formation of the external genitalia, rectal strictures and ulceration. The anorectal syndrome is an inevitable sequelae in both the sexes when the perirectal glands are involved either by direct or retrograde extension of the infection. Hematogenous spread of the organisms results in systemic infection. Persistence of LGV in the tissues or repeated infection by the same or related biovars may also be important in developing systemic disease.<sup>69</sup> The tissue damage in LGV is caused by a cell-mediated hypersensitivity response to chlamydial antigens.<sup>70</sup> Both cell-mediated and humoral immune responses are observed within 1–2 weeks of infection and correspond to the appearance of chlamydial cytoplasmic inclusions within the tissue phagocytes. The host immunity inhibits chlamydial multiplication, but may not eliminate the organism, resulting in a state of latency.<sup>47</sup>

## Clinical Features

The clinical presentation varies according to the sex of the patient, mode of sexual contact (vaginal or anal sex), and the stage of the disease. LGV is a chronic and progressively destructive disease. The clinical features, grouped conventionally into different stages, comprise of a primary stage, secondary stage (inguinal syndrome), and tertiary stage (genito-anorectal syndrome) (Table 41.1). Apart from these symptomatic stages, there are indications that in MSM LGV disease can remain asymptomatic.<sup>15,16</sup> Since the overall majority of these cases were HIV positive, compromised immunity could have caused the absence of symptoms. The frequency of asymptomatic LGV cases is debated.<sup>71</sup>

### PRIMARY STAGE

The average incubation period is 7–12 days, but may be as long as six months. The primary lesion may be an asymptomatic transient papule, pustule, herpetiform ulcer, or nodular ulceration (Fig. 41.1). Non-specific urethritis with thin, muco-purulent discharge is observed in 5% of males and 15% of females, and balanitis and balanoposthitis are reported in 2% of males.<sup>36</sup> The primary lesion occurs usually over the coronal sulcus, followed by frenulum, prepuce, penile shaft, urethra, glans penis, and scrotum in men and on the posterior vaginal wall, fourchette, posterior lip of the cervix, or the vulva in women. Cervicitis may also be a common manifestation of primary LGV.<sup>72</sup> The infection may extend proximally producing parametritis, endometritis, or salpingitis. In MSM, primary rectal inoculation produces bloody anal discharge, diarrhea and cramps.<sup>1</sup> Primary lesions of the

**Table 41.1:** Clinical Spectrum of LGV

Manifestations	Complications
<b>Primary stage</b> Transient papule, pustule, herpetiform ulcer, nodular ulceration, non-specific urethritis, balanitis, balanoposthitis, bubonulcus, cervicitis, salpingitis, parametritis	Phimosis, labial edema, infertility
<b>Secondary stage</b> (inguinal syndrome) Severe proctitis, bubo formation, inguinal multilocular abscess, Groove sign of Greenblatt	Sinus tracts, frozen pelvis, infertility, systemic arthritis, pneumonia, hepatitis, perihepatitis, meningoencephalitis, endocarditis, spondylitis, ocular inflammatory disease
<b>Tertiary stage</b> (genito-anorectal syndrome) Genital syndrome, anorectal syndrome, proctitis, proctocolitis	Genital elephantiasis, ramrod or saxophone penis, esthiomene, vaginal stenosis, urethral strictures, fistulae (recto-vaginal, urethro-vaginal, vulval), rectal strictures, stenosis, abscess formation (perirectal, ischioanal, suprapubic), rectal adenocarcinoma, lymphorrhoids
<b>Urethro-genito-perineal syndrome</b>	Papillary genital growths, perineal sinus
<b>Ocular manifestations</b>	Mixed papillary-follicular conjunctivitis, episcleritis, corneal ulcers, iritis, iridocyclitis
<b>Cutaneous manifestations</b>	Id eruption—transient generalized exanthemata, papules, pustules, nodules, urticaria, scarlatiniform eruption, erythema multiforme, erythema annulare centrifugum, erythema nodosum, photoallergic dermatitis
<b>Others</b>	LGV tonsillitis, pharyngitis, cholecystitis



**Fig. 41.1:** Primary lesion of lymphogranuloma venereum.

mouth, pharynx or tonsils can result from oral sexual exposure and typically heal within a period of one week without scar formation.<sup>28,73</sup> The primary stage lesion occurs in only 30% of heterosexual men and less often in women, although associated local edema may produce phimosis or swelling of the labia.<sup>1</sup> Rajam and Rangiah did not observe any primary lesion in 68.7% of the male and 58% of female LGV patients. In a study by Scieux et al.,<sup>74</sup> only five of the 27 LGV cases (18.5%) were able to recall having a primary lesion.

In this stage, a cord-like lymphangitis of the dorsal penis may develop, also known as sclerosing lymphangitis. This progresses to form a solitary, large, tender lymphoid nodule or “bubonulus” that may rupture to form sinuses or fistulae.<sup>75</sup>

## SECONDARY STAGE (INGUINAL SYNDROME)

The second stage begins within 2–6 weeks after the onset of primary lesion, but may be delayed for as long as 4–6 months. It is characterized by enlarged and tender regional lymphadenopathy or “Bubo.” The location of lymph node involvement is directly related to the site of the primary lesion (Table 41.2). Lymphadenitis of the submaxillary and cervical glands occurs if the site of primary inoculation is the mouth during receptive oral sex. Inguinal lymphadenopathy occurs if the primary lesion involves the anterior vulva, penis, anterior urethra or anus. Perirectal and deep iliac lymph nodes are enlarged in females if the primary lesion occurs on the posterior vulva, vagina, cervix, or rectum. Seventy five percent of all cases have simultaneous involvement of the deep iliac group of lymph nodes. In one-third of the patients, especially in heterosexual men but also in MSM in the current LGV epidemic in Western society, enlargement of the inguinal lymph nodes above, and the femoral lymph nodes below Poupart’s (inguinal) ligament occurs, resulting in the characteristic “Groove sign of Greenblatt” (Fig. 41.2).<sup>30,76</sup> The inguinal bubo is unilateral in two-third of the cases.<sup>30</sup> As it enlarges, the patient experiences severe pain in the groin and difficulty in walking. In 1–2 weeks, periadenitis sets in and the glands become matted, fixed and adherent to the overlying skin. The lymph nodes undergo necrosis and coalesce to form a multilocular abscess with edema and erythema of the overlying skin. Impending rupture is characterized by livid color (‘blue balls’) of the overlying skin. One-third of the abscesses rupture to form multiple sinus tracts discharging thick, tenacious, yellowish pus for weeks to months. Healing occurs leaving behind contracted scars in the inguinal region. Two thirds of the buboes involute spontaneously.

**Table 41.2:** Lymphatic Involvement Based on Site of Primary Infection

Site of primary lesion	Group of lymph nodes involved
Penis, anterior urethra, anterior vulva, anus	Superficial and deep inguinal
Posterior urethra, rectum, vagina, cervix	Deep iliac, perirectal
Mouth, pharynx	Deep iliac, perirectal, retrocrural, lumbosacral
Hands	Submaxillary, cervical
	Axillary



**Fig. 41.2:** Groove sign of Greenblatt.

Bubonic relapse occurs in about 20% of untreated cases. Inguinal lymphadenopathy occurs in only 20–30% of women with LGV. Primary involvement of the deep iliac or perirectal lymph nodes is more common in women. This involvement may produce symptoms of lower abdominal or back pain, often mistaken for acute appendicitis or tubo-ovarian abscess. When pelvic lymph nodes are involved, cystitis and urinary retention may occur. Perilymphangitis leads to formation of adhesions with the surrounding pelvic organs resulting in “frozen-pelvis.”<sup>30</sup> In the second stage, patients develop constitutional symptoms such as low-grade fever, chills, malaise, myalgia, and arthralgia. Systemic spread results in arthritis, pneumonitis, hepatitis, perihepatitis, meningoencephalitis, endocarditis, spondylitis, and ocular inflammatory disease. Cutaneous involvement in the form of erythema nodosum, erythema multiforme, or erythema annulare centrifugum may also occur.<sup>77</sup>

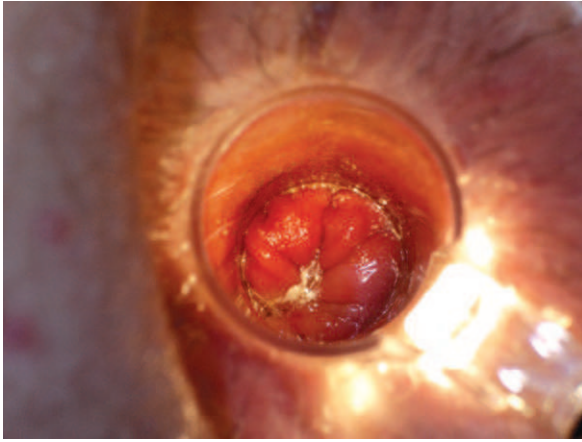
## SECONDARY STAGE (LGV PROCTITIS)

LGV proctitis, as occurs often in MSM, is characterized by perianal ulcers (Fig. 41.3) severe symptoms like anal cramps,



**Fig. 41.3:** Perianal ulcers of lymphogranuloma venereum proctitis.





**Fig. 41.4:** Proctitis due to lymphogranuloma venereum.

tenesmus, pain, bloody discharge, and constipation occur due to edema of the mucosal lining (Fig. 41.4) and underlying tissue. Normally LGV proctitis is not accompanied by lymphadenopathy noticeable upon physical examination. However, on radiologic imaging, lymphadenopathy in the pelvic area can be identified. In the present LGV epidemic among MSM, a considerable number of the patients with LGV proctitis are asymptomatic at the time of diagnosis, possibly due to the HIV co-infection which accompanies most infections.

### TERTIARY STAGE (GENITO-ANORECTAL SYNDROME)

This stage develops in 25% of untreated patients, predominantly in women who remain asymptomatic in the previous two stages, or in MSM who engage in receptive anal intercourse. In heterosexual men, it may occur by lymphatic spread from the posterior urethra. In women, the rectal mucosa may be directly inoculated during anal intercourse, by contamination with infectious vaginal secretions, or by lymphatic spread from the cervix and posterior vaginal wall. The persistence of infection in the anogenital tissue provokes a chronic inflammatory response causing procto-colitis, perirectal abscesses, fistulae, strictures and rectal stenosis, as well as hyperplasia of the intestinal and perirectal lymphatics leading to “lymphorrhoids.”<sup>78</sup>

### Genital Syndrome

Hyperplastic ulcerative changes may occur in the genitalia of both sexes, more commonly in women.<sup>79</sup> In men, chronic bilateral inguinal lymphadenitis leads to penile and scrotal elephantiasis, approximately 1–20 years after infection. It may affect only the prepuce, penile shaft, scrotum, or the entire external genitalia. The genital tissue becomes indurated and deformed. The penis becomes solidified giving rise to “ramrod penis.” It may sometimes be twisted resembling a saxophone (Fig. 41.5).<sup>80</sup>

Vascular compromise results in large destructive ulcers or occasionally superficial ulcers with irregular, serrated edges.

In women, chronic progressive lymphangitis and inguinal and pelvic adenitis leads to chronic edema, sclerosing fibrosis of the



**Fig. 41.5:** LGV in a man—saxophone penis.

subcutaneous tissue, elephantiasis, and chronic genital ulceration, referred to as *esthiomene* (Greek; ‘eating away’). It involves the labia, vulva, and clitoris, which gradually become enlarged. The size may vary from mere tumefaction of the lips to large, pendulous, multilobulated, unsightly masses of hypertrophied tissue hanging down and obstructing the vulval cleft (Fig. 41.6). The external surface of the labia majora, genito-crural folds, fourchette, urethral orifice, root of the clitoris, and perineum develop ulceration. These ulcers may be localized, large and superficial, or perforating. Rarely, penoscrotal elephantiasis due to LGV can occur in men also.<sup>79</sup> Genital sclerosis and ulceration result in serious sequelae. In women, it leads to vaginal stenosis, urethral strictures, and recto-vaginal, urethro-vaginal, vulval, or urinary fistulae. In a retrospective study conducted in Nigeria, LGV was found to be responsible for 0.55% of urinary fistulae in women.<sup>81</sup> In men, the complications include urethral strictures, prostatitis, seminal vesiculitis, and epididymo-orchitis.<sup>30</sup>

### Anorectal Syndrome

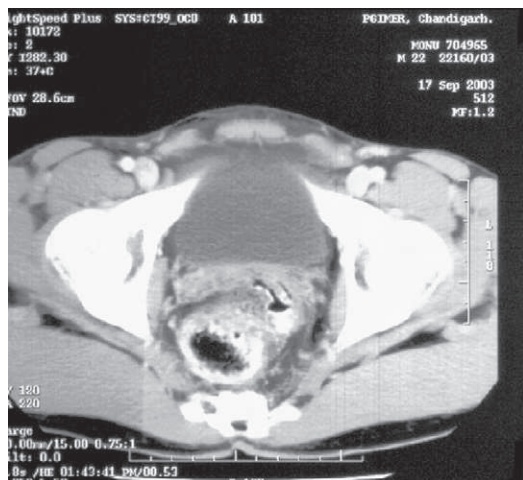
Chronic inflammation of the pelvic, perirectal and anorectal tissues leads to hyperplastic ulcerative changes in the anorectal mucosa. The infection is usually confined to the lower 8–10 cm of the anorectal region especially the portion below the peritoneal reflection, but may occasionally spread to the bowel as far as the transverse colon.<sup>78</sup> The condition begins as localized or diffuse edema of the anorectal mucosa causing pruritus and rectal discharge. On per rectal examination, localized or diffuse



**Fig. 41.6:** LGV in a woman—esthiomene originating from clitoris. Courtesy: Dr. Usha Gupta, Jabalpur, India and Dr. Somesh Gupta, Chandigarh, India.

pebbled appearance of the mucosa is felt due to enlarged and infected anorectal and pararectal lymph nodes. Subsequently, the mucosa becomes hyperemic and friable, and bleeds on manipulation. Proctoscopy reveals multiple, discrete, superficial ulcerations which are subsequently replaced by granulation tissue. Chronic proctocolitis follows with the formation of non-caseous granulomas and crypt abscesses. Symptoms of proctocolitis include fever, rectal pain, tenesmus, and a mucoid blood-stained discharge, which turns mucopurulent due to secondary infection by the endogenous bowel flora.<sup>82,83</sup>

The inflammatory process involves all layers of the bowel wall (Fig. 41.7). Over a period of 3–6 months, it is gradually replaced by fibrous tissue. As a result, the anorectal mucosa becomes rugose and rigid. The fibrous tissue contracts over a period of months to years leading to formation of rectal strictures and rectal stenosis.



**Fig. 41.7:** Contrast-enhanced computerised tomography scan of the pelvis of a patient with anorectal-genital LGV showing mural thickening of the rectum with presence of perirectal stanching. There is loss of the fat plane between the rectum and the left seminal vesicle. The patient complained of constipation and difficulty in defecation. Courtesy: Dr. Naveen Kalra, Chandigarh, India.

Rajam and Rangiah have described three types of strictures: annular, tubular and funnel-shaped. Annular strictures are the most common type (64%), usually situated 2–5 cm above the ano-cutaneous junction. They may be rigid and non distensible, or resilient and diaphragmatic. The proximal mucous membrane is ulcerated while the distal end is usually normal. In the end, the ulcers can lead to the perforation of the bowel wall and cause a peritonitis. Patients with this type of stricture experience chronic constipation, recurrent attacks of ileus with colic, abdominal distension, weight loss, and passage of “pencil” stools. In the tubular type, the entire bowel length below the pelvi-rectal junction is converted into a rigid, narrow tube with multiple constrictions along its length. In the funnel type, there is progressive narrowing from below upwards with the upper limit at the ampula of rectum. The anorectal and pararectal lymph nodes below the stricture suppurate to form perirectal and ischio-rectal abscesses. Supralelevator abscess formation mimicking rectal cancer has also been described.<sup>84</sup> These abscesses can rupture causing fistulae. Rectal adenocarcinoma may develop in 2–5% of patients with long-standing rectal strictures.<sup>85</sup> Lymphatic and venous obstruction of the lower rectum by the fibrotic process produces perianal outgrowths composed of dilated lymph vessels with perilymphatic inflammation, referred to as “lymphorrhoids” and mimicking perianal condylomata.

### Urethro-genito-perineal Syndrome

Long-standing disease in women results in papillary growths on the mucosa of the urethral meatus. It causes dysuria, frequent urination, urinary incontinence, and perimeatal ulceration. In men, penile, scrotal, or perineal sinuses may develop with or without urethral stenosis.

### OCULAR MANIFESTATIONS

Eye involvement may occur at any stage of the disease due to autoinoculation with the infectious discharge. The condition is commonly caused by *C. trachomatis* biovar L2 and is analogous to Parinaud oculoglandular syndrome. It manifests as mixed papillary-follicular conjunctivitis accompanied by submaxillary and posterior auricular lymphadenopathy. A hypersensitivity reaction to the antigen presenting as bilateral conjunctivitis, episcleritis, keratitis, or iritis, and occurring in association with the inguinal or anorectal syndrome has also been reported.<sup>1</sup>

### CUTANEOUS MANIFESTATIONS

Cutaneous lesions are attributed to a hypersensitivity reaction to the LGV antigens (id eruption or ide reaction) and present as transient generalized exanthemata, widespread papules, pustules, nodules, scarlatiniform eruption, urticaria, erythema multiforme, erythema nodosum, and erythema annulare centrifugum.<sup>77</sup> A photoallergic dermatitis (probably due to an allergic reaction to the toxins), manifesting as recurrent itchy papular and papulo-vesicular eruptions on sun-exposed regions has been described.<sup>77</sup> It usually occurs in association with the inguinal or anorectal syndrome.



## OTHER EXTRAGENITAL MANIFESTATIONS

LGV tonsillitis and primary LGV of the mouth and pharynx may occur as a result of receptive oral sex.<sup>39,73</sup> It is associated with cervical or submaxillary lymphadenopathy. Axillary lymphadenopathy has been reported due to accidental infection among doctors, nurses, or laboratory workers handling infectious material.<sup>1</sup> Cases of supraclavicular lymphadenitis in association with mediastinal lymphadenopathy and LGV pericarditis have been reported.<sup>86</sup> Chronic cholecystitis secondary to LGV has been documented with the organism isolated from gall bladder wall. There are also reports of LGV presenting as a psoas abscess.<sup>87</sup> Recently, a case of reactive arthritis has been reported occurring after the development of proctitis due to *C. trachomatis* L2b biovar.<sup>88</sup>

## LGV and HIV and Hepatitis C

In the current LGV epidemic among MSM, the majority are co-infected with HIV (approximately 80%),<sup>15–17,71,89,90</sup> but hepatitis C is also found in up to 18%.<sup>15,91</sup> Until recently hepatitis C was not considered as a sexually transmissible pathogen. Nonetheless, there are strong indications that in the current LGV epidemic among MSM, hepatitis C infections were acquired through high risk sexual contacts.<sup>92</sup> Because LGV is an ulcerative disease, the transmission of blood borne diseases like hepatitis C but also HIV is possibly facilitated. During a retrospective analysis of 27 cases of LGV seen in a Paris hospital, 6 cases with concomitant HIV infection were found.<sup>74</sup> However, HIV appeared to have no effect on the clinical presentation in these cases. Similarly, Heaton et al.<sup>93</sup> reported a case of a HIV-positive pregnant woman with uncomplicated LGV. In a South African study comprising 45 HIV-infected patients compared to 8 non-HIV-infected patients with LGV the clinical presentations of LGV were similar for both groups.<sup>37</sup>

A few studies have demonstrated reactivation of latent LGV with the development of multiple groin abscesses in HIV-positive patients.<sup>30</sup> Buus et al.<sup>94</sup> reported an atypical presentation of Parinaud oculoglandular syndrome consisting of unilateral follicular conjunctivitis with superior marginal corneal perforation in association with preauricular and inguinal lymphadenopathy due to *C. trachomatis* biovar L2 in an HIV-positive patient. The patient responded well to topical cefazolin and gentamicin, oral tetracycline, and surgical management. In both HIV-positive and negative cases, the diagnosis can be established by high chlamydial complement fixation antibody titers (>1:64).<sup>95</sup> Yet, Nucleic Acid Amplification Tests (NAAT) are the preferred diagnostics nowadays (see below). Centers for Disease Control and Prevention recommends the same treatment regimen for LGV in HIV-positive and negative patients.<sup>96</sup>

## Differential Diagnosis

The diverse presentations of LGV make it extremely difficult to establish a definitive diagnosis by clinical examination alone. The variability of presentation during different stages of disease

evolution poses a great challenge in differentiating it from other dermatological and sexually transmitted diseases (Table 41.3).<sup>97–100</sup>

The primary stage, characterized by an evanescent, painless papule, erosion or ulcer, is often missed by the clinician. It may simulate genital herpes, primary syphilis, chancroid or traumatic ulceration. A mucopurulent urethritis noted in a few instances of LGV, is often mistaken for non-specific urethritis or gonorrhea. A balanoposthitis like picture mimicks bacterial, candidal or traumatic balanoposthitis.<sup>30</sup> In a report by Zweizig et al.,<sup>101</sup> the clinical presentation and tomographic findings in a patient with primary inoculation LGV of the cervix were suggestive of cervical cancer.

The second stage of LGV manifests as regional lymphadenitis and perilymphangitis with bubo formation. It is usually associated with fever and constitutional symptoms. The involved lymph nodes are tender, matted and form multilocular abscesses that rupture to form multiple discharging sinuses. The primary genital lesion is usually absent at this stage. This condition poses a diagnostic dilemma and is often confused with the bubo of chancroid, syphilis, genital herpes, plague, tularemia, tuberculosis lymphadenitis, cat-scratch disease, septic lymphadenitis, Hodgkin disease, incarcerated inguinal hernia, or psoas abscess.<sup>102</sup>

In the tertiary stage, genital elephantiasis may mimic filariasis, tuberculosis, fungal, or parasitic infection, granuloma

**Table 41.3:** Differential Diagnosis of LGV

<b>Primary stage</b>
<ul style="list-style-type: none"> <li>• Genital herpes</li> <li>• Primary syphilis</li> <li>• Chancroid</li> <li>• Traumatic ulcer</li> </ul>
<b>Secondary stage (inguinal syndrome)</b>
<ul style="list-style-type: none"> <li>• Chancroid</li> <li>• Syphilis</li> <li>• Genital herpes</li> <li>• Plague</li> <li>• Tularemia</li> <li>• Tuberculosis</li> <li>• Cat-scratch disease</li> <li>• Septic lymphadenitis</li> <li>• Hodgkin disease</li> <li>• Incarcerated inguinal hernia</li> <li>• Psoas abscess</li> <li>• Kikuchi-Fujimoto syndrome</li> </ul>
<b>Tertiary stage - Genital elephantiasis</b>
<ul style="list-style-type: none"> <li>• Filariasis</li> <li>• Tuberculosis</li> <li>• Fungal infection</li> <li>• Parasitic infection</li> <li>• Granuloma inguinale (Donovanosis)</li> <li>• Toxemia of pregnancy</li> <li>• Anorectal syndrome</li> <li>• Inflammatory bowel disease (esp. Crohn disease)</li> <li>• Rectal stricture</li> <li>• Malignancy</li> <li>• Trauma</li> <li>• Actinomycosis</li> <li>• Schistosomiasis</li> </ul>



inguinale (pseudo-elephantiasis), or transient vulvar elephantiasis with toxemia of pregnancy.<sup>30</sup> The clinical and histologic picture of early LGV proctocolitis is similar to that seen in inflammatory bowel disease.<sup>30</sup> LGV proctitis has been mistaken for Crohns disease which has led to delay in the correct diagnosis, and suboptimal treatment.<sup>89,103</sup> The rectal strictures of LGV may resemble those caused by trauma, actinomycosis, tuberculosis, schistosomiasis, or adenocarcinoma of the rectum.

## Laboratory Diagnosis

### STANDARD DIAGNOSTIC PRACTICE FOR CLINICAL PURPOSES

LGV is a complex disease with varied clinical manifestations and is difficult to diagnose on clinical grounds alone. The gold standard diagnosis of LGV is made on the detection of biovar specific bacterial DNA in rectal specimens (in case anorectal LGV is suspected) or in genital ulcers or bubo aspirate (in case inguinal LGV is suspected), although the organism is difficult to detect in bubo aspirates. It is advised for budgetary reasons to follow a two-step procedure. First, a commercially available pan *C. trachomatis* Nucleic Acid Amplification Test (NAAT) can be used to screen suspected samples.<sup>104</sup> Although no commercially available tests are approved for extra genital sites, a large body of literature supports the use of these tests for the detection of rectal chlamydia infections.<sup>16,105–107</sup> If *C. trachomatis* is found, LGV biovar specific DNA needs to be sought. For this purpose, several “in house” NAAT tests have been developed. These tests can discriminate different *C. trachomatis* serotypes based on specific epitopes on the major outer membrane protein A (MOMP).<sup>108</sup> Firstly, a real-time polymerase chain reaction based test that specifically detects all *C. trachomatis* LGV biovar strains developed by Morré et al.<sup>7</sup> The second test is a real-time quadriplex PCR assay that incorporates an LGV specific target, a non-LGV-specific target sequence, a *C. trachomatis* plasmid target, and the human RNase P gene as an internal control as described by Chen et al.<sup>6,109</sup> These methods discriminate between LGV and non-LGV biovar types only, which is sufficient for clinico-diagnostic purposes. Recently, commercial tests have become available, which can discriminate 15 different *C. trachomatis* biovars, including the different LGV specific ones.<sup>110</sup> These tests can also be used to diagnose LGV.<sup>111</sup> In case molecular diagnostic test facilities are not at hand a presumptive LGV diagnosis can be made using chlamydia specific serological assays. A high antibody titer in a patient with complaints suggestive of LGV supports the diagnosis. Nonetheless, a low titer does not rule out LGV, nor does a high titer in a patient without LGV symptomatology prove LGV infection.<sup>16,43</sup> Although it has been stated that an elevated chlamydia specific IgA and IgG titer is associated with LGV,<sup>112</sup> asymptomatic LGV infections require LGV specific NAAT assays for accurate diagnosis.<sup>113</sup>

### GENOME SEQUENCE ANALYSIS NOT FOR DIAGNOSTIC PURPOSES

Recent advantages in genome sequence analysis has been used to elucidate the origin of LGV outbreaks and the specific clinical characteristics of LGV.<sup>114</sup> Multilocus Sequence Typing (MLST) is a genotyping method based on amplification and sequencing of several genetic regions.<sup>115</sup> It has been used to deduce the nature and origin of the LGV outbreak among MSM in Europe.<sup>116</sup> In combination with single nucleotide polymorphism (SNP) analysis, MLST is a promising tool for epidemiologic and evolutionary studies of LGV populations worldwide.<sup>117</sup>

### HEMATOLOGICAL INVESTIGATIONS

The hematological and biochemical investigations suggestive of LGV include mild leukocytosis, monocytosis, and eosinophilia, increase in total serum proteins due to raised IgG, IgA and IgM levels with reversal of the albumin:globulin ratio, and raised erythrocyte sedimentation rate (ESR).<sup>118</sup>

### FREI TEST

The Frei test is based on a delayed type hypersensitivity reaction on LGV specific antigen, but has become obsolete now and the antigen is not available commercially. It is an intradermal test for the diagnosis of present or past LGV infection and remains positive for life. It shows cross-reactivity with other chlamydial infections such as psittacosis, and with cat-scratch disease.

### CHLAMYDIA CULTURE

#### Specimen Collection

Appropriate sites for specimen collection for chlamydia isolation are the rectal mucosa, urethra and cervix. In bubo pus the correct diagnosis is often missed due to the high concentrations of digesting enzymes which break down bacterial antigens and often interfere with current diagnostic tests. Rayon and PET fiber swabs are superior to cotton or calcium alginate. Due to the invasive nature of the L biovar causing LGV disease, the best material for LGV diagnostics are biopsies including both mucosa and underlying connective tissue from infected sites.<sup>119</sup> Since obtaining a biopsy comprises an invasive procedure it cannot be performed in all settings, and swabs from mucosal linings are the second best option. The cytobrush, a small brush on a wire or a plastic shaft, is an excellent device for collecting cervical or rectal specimens. It collects more material compared to non-rigid devices and increases the sensitivity of Chlamydia detection methods.

### Sampling Sites

- **Bubo:** The bubo pus is collected by aspirating with a wide-bore needle if it is fluctuant. If it is not fluctuant, sterile saline

is injected and then aspirated. Before inoculation on tissue culture, the specimen is homogenized in the culture medium to obtain a 10–20% (w/v) suspension and inoculated in a 1:10 to 1:100 dilution.

- **Rectum:** Specimens are collected using an anoscope for the direct visualization of erythematous, friable mucosa, and areas of mucopus. The swab is inserted 3 cm into the anal canal and rotated for 10 seconds to collect exudate from the crypts just inside the anal ring. Since the rectal specimens frequently cause contamination or cytotoxicity in tissue culture, it is advisable to sonicate them prior to inoculation.
- **Urethra:** A thin swab is introduced 3–4 cm into the urethra and the mucosa is scraped by rotating the swabs for 5–10 seconds.
- **Cervix:** Before obtaining the specimen, the exocervix is cleaned to remove external secretions. The swab is inserted 2 cm into the cervical canal and rotated for 10 seconds to gently scrape the epithelial cells.
- **Eye:** The eyelid is everted and epithelial cells are collected by rubbing a swab over the conjunctival mucosa.
- **Throat:** The specimen is collected from the region of tonsillar crypts and posterior pharynx.

## Specimen Transport

The specimens for tissue culture are inoculated and transported in cryovials containing 0.8–1 ml of the transport medium, such as sucrose phosphate medium or phosphate-buffered sucrose solution containing fetal calf serum and antimicrobial inhibitors. Immediate inoculation of the specimen (<2 hours) on to tissue culture cells yields the highest rate of success. If they are to be processed within 24 hours, specimens are refrigerated at 4°C immediately after collection. For longer periods (>24 hours), the specimen is frozen and stored at –70°C.

## Culture

Cell lines that have been widely used for *C. trachomatis* isolation include certain clones of HeLa 229, baby hamster kidney cells (BHK-21), and McCoy cells. The culture technique involves inoculation of clinical specimens into cycloheximide-treated McCoy cells (since cycloheximide reduces the metabolic activity of eukaryotic cells) or DEAE treated HeLa cells.<sup>9</sup> The cells are incubated at 36–37°C for 72 hours, stained with 0.5 ml of 5% iodine solution for 5–10 minutes and examined microscopically for the presence of typical dark-brown inclusions surrounded by a halo. Some laboratories prefer Giemsa staining, since Giemsa-stained cells can be visualized by dark-field microscopy.<sup>120</sup> An alternative is use of the immunofluorescence technique with fluorescein-labeled monoclonal antibodies. It is a very sensitive method, especially in asymptomatic cases, since greater number of inclusions can be detected in a short period.<sup>121</sup>

The reported recovery rate by culture from the buboes, genital or rectal tissue varies from 24–30%.<sup>122</sup> LGV-Chlamydia can also

be isolated by inoculation in mouse brain or the yolk sac of chick embryo with recovery rates of 98% and 78%, respectively.<sup>123</sup> The biovar L2 has also been isolated from an infected bubo in an endothelial cell culture system.<sup>124</sup>

## CYTOLOGY

The elementary bodies (EBs) and reticulate bodies (RBs) can be visualized in tissue scrapings by staining with Giemsa, Brown–Hopp hematoxylin and eosin, Warthin–Starry, Grocott methenamine silver, or phosphotungstic acid hematoxylin stains.<sup>61</sup> In the Giemsa stained smears, EBs appear purple, while the intracytoplasmic inclusions in epithelial cells containing RBs are basophilic and stain blue. Cytoplasmic areas around the inclusions appear grey whereas the nucleus stains pink. The development of fluorescein-labelled monoclonal antibodies directed against species-specific epitopes of major outer membrane protein also allows direct visualization of EBs.<sup>125</sup> It is a rapid diagnostic test, but interpretation of individual specimens is laborious and is recommended only when a relatively low number of specimens have to be processed. Chlamydial EBs appear as bright apple-green pin-points and the cells are counter stained red. Any particle, debris or artefact showing yellow-green fluorescence is a source of false-positive results. This technique shows acceptable accuracy for symptomatic patients, but lacks sensitivity in asymptomatic subjects who harbor lower numbers of organisms at sites of infection. Immunohistochemical examination can be performed using the avidin-biotin method.<sup>3</sup> This modality has a lower sensitivity as compared to culture and the presence of mucus, cell debris, microorganisms, and a small number of infected cells hamper microscopic diagnosis.

## HISTOPATHOLOGY FOR IDENTIFICATION OF CHLAMYDIA IN INFECTED LYMPH NODES

The major diagnostic feature of LGV in the lymph nodes is the presence of vacuolated macrophages with intravacuolar organisms. The RBs line the vacuolar membrane and the smaller EBs are scattered throughout or are clumped inside the vacuole. These vacuoles, although most prominent at the margin of suppuration, may be present in the centre of the abscess or lie within the periphery of the mantle of lymphoid follicles. Clusters of monocytoid B-cells assemble at the periphery, particularly in subcapsular or paratrabeular spaces. Microabscesses develop at the junction of the vacuoles and B-cells, or within clusters of B-cells. In well-formed secondary follicles, fibrin deposits form intercellular networks from the margin of affected germinal centers inwards, often in a crescent shape. At the margin of the follicle, monocytoid B-cells expand the subcapsular and paratrabeular spaces. Macrophages intersperse among the B-cells, and abscesses expand within or adjacent to B-cells. Expanding abscesses penetrate the mantle and impinge upon the germinal center. A wreath of macrophages forms around the abscess with an outer

collar of B-cells. Pools of extracellular organisms lie inside the margin of the abscess. Also adjacent to the abscesses, the vascular endothelial cells are prominent and narrow the lumen. In other areas of the lymph node, there are foci of hemorrhage. The capsule may become focally thickened. Electron microscopy reveals small spherical intracytoplasmic vacuoles dividing by binary fission. These organisms appear in three different forms. The largest, 1.9  $\mu\text{m}$  in diameter, have evenly distributed ribosomes surrounded by cytoplasmic membrane. In larger vacuoles, 0.2–0.4  $\mu\text{m}$  diameter microorganisms with an eccentrically located electron-dense nucleoid structure, coarse electron dense ribosomes and well-defined cell wall and cytoplasmic membrane are present, and these are identical to EB. Intermediate bodies have a centrally condensed nuclear region separated from peripherally located ribosomes by an electron-transparent space.

## ANTIGEN DETECTION

### Enzyme Immunoassays (EIAs)

This method is suitable for antigen detection in ulcer scrapings or bubo aspirates but not for rectal samples. It has a sensitivity of 75–80%.

### Rapid Assays

Rapid assays, or “point of care tests” for *C. trachomatis* antigen detection, giving results within 30 minutes, have recently been developed.<sup>126</sup> These assays require a minimum of direct “hands on” manipulation, need no sophisticated equipment, and permit rapid diagnosis in field conditions. Several rapid assays have been made commercially available for the detection of urogenital *C. trachomatis* infections. None discriminates between LGV and non-LGV biovars, which makes their use for LGV diagnostics limited. Moreover, the sensitivity of most of these tests are disappointingly low to detect urogenital Chlamydia infections.<sup>126</sup> Better results with a sensitivity up to 80% have been claimed by some of the newer versions of these “point of care tests.”<sup>127</sup> To date, no information is available on the diagnostic use of these rapid assays for the detection of LGV infections.

## ANTIBODY DETECTION

The serological methods have limited use in the diagnosis of acute LGV infection.<sup>128</sup> While the detection of high levels of IgG antibody (titer of 1:256) may support the diagnosis of LGV, the presence of IgM (serum titer of 1:32) is more valuable. Diagnostic evidence can be obtained by demonstration of seroconversion in paired sera. Antibodies to LGV-Chlamydia can be detected by various serologic tests.

### Complement Fixation Test (CFT)

This is the most widely used serologic test.<sup>129</sup> It becomes positive after 1–3 weeks of infection. A CFT titer of 1:64 indicates active LGV infection and is observed in 50% of the patients.

Occasionally, high titers may be found in asymptomatic patients and those with other chlamydial infections. This test has a sensitivity of 80% for LGV. It does not reflect the efficacy of treatment or the progress of disease.

### Microimmunofluorescence Test (MIF)

It is the most accurate serologic assay.<sup>8</sup> It uses formalin-fixed EBs grown in yolk sac as antigen. During the active phase of LGV, patients show high levels of IgM (titers > 1:32) and IgG (titers > 1:512) with the antigen type of the infecting strain and much lower cross-reactivity with other *C. trachomatis* strains. However, preparation of the antigen for this test is complex and laborious and to date, the use of MIF has been limited to a few research laboratories. Ready-to-use antigens are not widely available.

### Single L-type Chlamydial Fluorescence Test

This test utilizes chlamydial inclusions from a tissue culture infected with LGV-L2 strain.<sup>130</sup> It is more sensitive than CFT but crossreacts with the other biovars of *C. trachomatis* and *C. pneumoniae*. The test may be useful for screening populations for epidemiological purposes, but not for diagnosis.

### Radioisotope Precipitation Test (RIP)

This test is more sensitive than the MIF test.<sup>70</sup> In this procedure, antiglobulin is used to precipitate radioactive-labeled and soluble chlamydial antibody. The proportion of radioactivity removed from the system is a measure of the amount of antibody present.

### Neutralizing Antibody Test

In this test, serum is combined with virulent mouse brain emulsions and inoculated intracerebrally.<sup>70</sup> If the test serum contains LGV antibody, the inoculated mixture does not cause meningo-encephalitis.

### Immunoperoxidase Test

It is a simple and rapid test for detecting *C. trachomatis* specific IgG and IgA antibodies.<sup>13</sup> IgG titer greater than 1:128 and IgA greater than 1:16 is suggestive of active infection. It has been found to be positive in 83.3% cases of LGV.

ELISA and counter immune electrophoresis (CIEP) are other serologic tests for the diagnosis of LGV.<sup>41,131</sup>

## IMMUNOTYPING OF ISOLATES (MONOCLONAL ANTIBODIES)

This is primarily of research interest, but may be used for epidemiological purposes. Biovar-specific monoclonal antibodies have been developed and two methods, microimmunofluorescence, and immunodot enzyme immunoassay, may be used as test procedures.<sup>132</sup> In a study, monoclonal antibodies raised against LGV biovars L1 and L3 were able to establish a diagnosis in 68% and 16% of cases, respectively.<sup>133</sup>



## RADIOLOGICAL INVESTIGATIONS

Computerized tomographic scan or magnetic resonance imaging of the abdomen and pelvis may be useful if retroperitoneal adenitis or an intra-abdominal abscess is suspected.<sup>1</sup> It may also help in assessing the extent of inflammation in rectum and anorectal stricture (Fig. 41.7). Lymphangiography does not outline buboes, but may demonstrate the extent of lymph node involvement. Barium enema may reveal elongated strictures in rectal LGV.

## Treatment

The goal of therapy is to eradicate the pathogen. Medical treatment is of immense value in the acute phase of the disease such as acute bubo, ulceration, draining sinuses, proctitis, and colitis.<sup>134</sup> Early and prompt treatment is essential to prevent disease transmission, serious complications, and mutilating sequelae. There is paucity of controlled double-blind treatment trials for LGV in the literature. The low incidence of the disease, its complex presentation and the natural history marked by spontaneous remissions and exacerbations have precluded any rigorous evaluation of management. Nevertheless, sporadic trials have shown successful use of sulfonamides,<sup>135</sup> tetracyclines,<sup>136</sup> minocycline,<sup>137</sup> and erythromycin<sup>138</sup> in the treatment of LGV. With early and prompt treatment, it has been shown that the duration of buboes is reduced, ulcers rapidly heal, sinuses cease to drain, and rectal discharges abate.<sup>134</sup> Prolonged treatment (at least for 3 weeks) is the norm and more than one course of therapy or alternating some of the antibiotics may be necessary for chronic cases. It has been shown that L biovar *C. trachomatis* RNA can persist for up to 16 days in LGV proctitis patients treated with doxycycline, whereas nucleic acid from non-LGV biovars was undetectable after 7 days.<sup>139</sup> On the basis of the known response of *C. trachomatis* to antibiotics in uncomplicated infections, the following recommendations have been made:

- **World Health Organization (2003):** Doxycycline, 100 mg orally twice a day × 2 weeks, or Erythromycin, 500 mg orally, 4 times a day × 2 weeks, or Tetracycline, 500 mg orally, 4 times a day × 2 weeks, or Sulfadiazine, 1 g orally 4 times a day × 2 weeks
- **Centers for Disease Control and Prevention (2010)<sup>96</sup>:** Doxycycline, 100 mg orally twice a day × 21 days, or Erythromycin, 500 mg orally 4 times a day × 21 days, or Azithromycin, 1 g orally once weekly × 3 weeks.
- **Other Treatment Modalities:** Minocycline, 300 mg orally initially, followed by 200 mg twice a day for 10 days has been successfully used in treating acute bubonic LGV and LGV proctocolitis.<sup>137</sup>
- Rifampicin, 450 mg in a single daily dose for 10 days has been found useful. Azithromycin, single 1 g oral dose is effective in uncomplicated infection.<sup>140</sup> An alternative regimen of azithromycin single 1 g orally with doxycycline, 100 mg twice a day for 7 days was also found useful.

- **Children and Pregnancy:** For pregnant and lactating women or children below 8 years, erythromycin stearate is prescribed.<sup>99</sup> In children, the dose is 7.5–12.5 mg/kg/dose four times a day for 2 weeks.

## SURGICAL TREATMENT

The chronic manifestations of LGV such as genital elephantiasis, vulval growths, esthiomene, or rectal strictures and stenosis do not respond to antibiotic therapy and require surgical intervention and plastic reconstruction. For buboes, hot fomentation may be advised. Fluctuant buboes are aspirated through the surrounding normal skin with a wide bore needle, and not incised.<sup>141</sup> Rectal strictures are dilated either manually or with elastic bougies at weekly intervals. When the stricture is impassable, a preparatory ileo-colostomy followed by proctocolectomy is a justifiable procedure.<sup>30</sup> Chronic intractable ulcerative lesions of the rectum may be treated by suitable single-stage surgical procedures, such as full skin cover by direct flaps, myocutaneous flaps, or sliding flaps (floating island).<sup>102</sup> A urethral stricture can be dilated with Lister's or Clutton's bougies.<sup>30</sup> Perianal and perirectal abscesses must be surgically drained. Surgical repair of recto-vaginal fistulae, esthiomene, and genital elephantiasis may be required. Polypoid excrescences of the vulva, pedunculated tumors or elephantiasic vulvae require local excision, and partial or total vulvectomy.

## FOLLOW-UP

Patients without anatomical deformations due to the LGV infection who have received the standard antimicrobial therapy do not require clinical follow up visits. In case of anatomical defects like fistulae, strictures or sinuses that possibly require surgical intervention need to be followed up until their complaints have been dealt with.

## PARTNER MANAGEMENT

Subjects who have had sexual contact with an LGV patient within 6 months before the onset of the patient's symptoms, or in case of asymptomatic cases at the time of diagnosis, should be examined, tested for chlamydial infection and promptly treated empirically.<sup>30</sup>

## Prevention

In endemic areas, LGV can be prevented by practicing safe sexual habits such as use of condoms and avoidance of casual sexual contact, particularly with sex workers. Enema use prior to receptive anal sex should be discouraged since it is associated with rectal chlamydial infections, and especially LGV proctitis.<sup>15</sup> Sexual contacts must be traced and promptly treated. Patients on antibiotic therapy should be monitored for recurring symptoms over a period of 6 months following antibiotic treatment.<sup>26</sup> Doctors and other healthcare workers must observe proper safeguards such as wearing gloves when touching infected sites or handling soiled dressings or other contaminated items. Health-

seeking behavior and health education of those at risk should be encouraged.

## Conclusion

LGV is a serious STI caused by the invasive *C. trachomatis* L biovar. The wide variety of symptoms ranging from acute inflammatory disease to chronic mutilating sequelae can cause a diagnostic dilemma for the clinician. Physicians should consider LGV in patients with inguinal lymphadenopathy, genital ulceration, fistulae, or anorectal complaints. Although it used to be confined to equatorial areas, an on going LGV epidemic among MSM in the Western world has emerged since 2003. There is a need for better and cheaper screening tools to detect cases in larger groups of individuals at risk. This is of importance to prevent complications in the individual patient and to halt transmission in the community. Shorter antibiotic courses than the present ones of 21 days are needed to increase patient compliance to the treatment but require large controlled clinical trials. Lastly, a deeper understanding of the microbial and immunological background of LGV infection could shed light on the invasive nature of the LGV biovars, which contrasts the inert infections caused by the non-LGV *C. trachomatis* biovars.

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# Chancroid

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## Introduction

Chancroid is a sexually transmitted infection (STI) of the genitoinguinal area caused by the bacterium, *Haemophilus ducreyi*. It manifests clinically with single or multiple, superficial, tender ulcers over the anogenital region. Painful inguinal lymphadenitis with or without bubo formation may occur in half of the patients. Chancroid is one of the major causes of genital ulcer disease (GUD), and constitutes an important cofactor in the transmission of HIV infection in many resource-poor countries of Africa, Asia, and Latin America.<sup>1</sup>

## Historical Aspects

According to Kampmeier, chancroid was first described in 1852 (France) by Ricord and Bassereau as *ulcus molle* differentiating it from the hard chancre of primary syphilis.<sup>2</sup> In 1889 Augusto Ducrey, a bacteriologist at the University of Naples, performed a series of autoinoculations on the forearms of patients with purulent material from their own genital ulcers, and established *H. ducreyi* as the etiological agent of chancroid.<sup>3</sup> Bezancon et al. are often credited for the first significant isolation of *H. ducreyi*.<sup>4</sup> Unna described the histopathology of chancroid, and observed clumps and chains of gram-negative rods in tissues.<sup>5</sup>

Ito introduced intradermal testing with *H. ducreyi* obtained both from culture and with pus from a chancroidal bubo in 1913. The appearance of a papule 8 mm or more in diameter between the 3rd and 7th day was considered confirmatory.<sup>6</sup> This was later validated by Reenstierna in 1921 at the Pasteur Institute, and the diagnostic value of the Ito-Reenstierna test was further evaluated by Greenblatt et al.<sup>7</sup> However, this test is now only of historical importance as the antigens are no longer available.

## Epidemiology

According to a World Health Organization (WHO) report, an estimated 7 million cases of chancroid occur annually across the globe.<sup>8</sup> The true global epidemiology is unclear since chancroid cannot be reliably differentiated from other GUDs on clinical

grounds and there is a lack of readily available diagnostic tests in most clinics. The disease however is prevalent worldwide, and endemic in many poor countries of tropical and subtropical regions with inadequate medical infrastructure, especially sub-Saharan Africa, Asia, and Latin America.<sup>9,10</sup>

The pattern of GUD is changing rapidly with studies from Africa revealing that GUD attributable to herpes simplex virus (HSV) type-2 infection is increasing, and that of *H. ducreyi* is decreasing in many areas.<sup>11</sup> A gradual decline in the prevalence of *H. ducreyi* was noted among patients attending an STI clinic in Durban (South Africa), from 35% in 1995 to 6% in 1998. During the same period, HSV-2 infection rose from 11% to 45%.<sup>12</sup> Since the mid-1960s, the incidence of chancroid has been decreasing in many parts of Africa and Asia, especially Kenya, Senegal, Philippines, and Thailand. This may partially be a consequence of intervention strategies targeting commercial sex workers (CSWs) and STI patients to prevent HIV transmission.<sup>1</sup> In Nairobi, Kenya, chancroid was endemic but now accounts for less than 10% of genital ulcers. The number of reported cases of chancroid has declined steadily in the USA from 4986 cases in 1987 to 143 cases in 1999.<sup>13</sup> More recent CDC statistics reveal that chancroid is disappearing in the United States, with only 23 cases reported nationwide in 2007.<sup>14</sup> In the United Kingdom, 378 new episodes of tropical GUD (combining chancroid, LGV, donovanosis) were seen at the genitourinary medicine clinics in 2008. England accounted for 367 (97%) episodes, of which 183 (almost 50%) were seen in London. These figures were mainly due to the recent epidemic of LGV.<sup>15</sup> Chancroid is rare in the Scandinavian countries and Australia.<sup>16,17</sup> Chancroid is endemic in some parts of India, and its prevalence has varied from 1.6% to 51.9% based on reports from different STI clinics.<sup>18–20</sup> The wide variation may be due to the lack of uniform diagnostic criteria besides diverse social, cultural, and religious practices prevailing in the local population. The prevalence of chancroid has been reported to be 22.4% among children below 14 years of age with STIs in Delhi.<sup>21</sup>

Chancroid is seen more frequently in the sexually active age group of 18–45 years. Men are more commonly affected, with



the male to female ratio exceeding 10:1 (varying from 1.6:1 to 53:1).<sup>22–24</sup> Important factors contributing to the gender disparity, may be the possibility of fewer women transmitting the infection to a large number of men through commercial sex, an asymptomatic carrier state in women,<sup>25</sup> and the concealed and subclinical nature of lesions on the female genitalia resulting in unhampered sexual activity. It also appears that an occlusive environment provided by the prepuce makes men more susceptible. A recent meta-analysis revealed that circumcised men were clearly at a lower risk of chancroid.<sup>26</sup>

The disease is almost always contracted through sexual contact, barring minor episodes where medical professionals acquire the infection on fingers through accidental inoculation. Plummer et al. have reported that the chances of acquiring infection during a single act of unprotected exposure from man to woman are as high as 63%.<sup>27</sup> In the absence of treatment, the duration of infection has been estimated to be 45 days in women, and it appears that the risk of transmission is much more with patients bearing visible lesions.<sup>28</sup> Fomites do not play a role in the transmission of the disease. There is no nonhuman reservoir for *H. ducreyi*, and it depends for its survival and propagation on sexual transmission. Individuals with poor hygiene and CSWs constitute a major source of infection. Alcoholism and cocaine abuse in the smoked form (“crack”) are also associated with an increased risk.<sup>29,30</sup>

## Biology

*H. ducreyi* is a pleomorphic, slender ( $1.2 \times 0.5 \mu\text{m}$ ), gram-negative, nonmotile, nonspore forming, and facultative anaerobic streptobacillus with rounded ends. It is a fastidious organism with complex nutritional requirements for its growth. It has some characteristic biochemical properties, which include a reaction positive for oxidase and alkaline phosphatase activity, and negative for catalase activity. It reduces nitrate to nitrite and requires hemin (X-factor) for growth. In liquid culture or tissue the organisms form parallel chains resembling “railroad tracks”, while on solid agar “schools of fish” and whorls appear which resemble “fingerprints”.<sup>31</sup> Recent genetic sequencing data has revealed that *H. ducreyi* is more closely related to the animal pathogens *Actinobacillus pleuropneumoniae* and *Mannheimia haemolytica* than to human pathogens in the Pasteurellaceae family. However, animal models of chancroid do not adequately simulate human infection, suggesting that *H. ducreyi* has deviated from other organisms to establish itself as a unique human pathogen.<sup>32</sup>

## Pathogenesis

The exact pathogenesis of ulcer formation in chancroid is not clear. The organisms appear to enter sites of trauma or abrasion where the integrity of skin is disrupted. The inoculum size has to be more than  $10^4$  to produce an infection.<sup>33</sup> Adherence of bacteria to the epithelial cells is mediated by pili, and the subsequent production of hemolysins and cytotoxins results in cell damage. Both cell-mediated and humoral responses occur to infection with chancroid. A delayed hypersensitivity reaction and recruitment of

peripheral blood mononuclear cells is seen in response to specific *H. ducreyi* antigens. The cell-mediated response to *H. ducreyi* infection is predominantly of Th-1 cells. Immunohistological studies have revealed a predominant mononuclear infiltrate consisting mainly of CD4+ and CD8+ T-lymphocytes, and monocytes with a conspicuous paucity of B-lymphocytes in the biopsy specimens of chancroid lesions. This predominant T-helper cell (Th1) response is consistent with the observation of increased levels of soluble interleukin-2 receptors in the urine and semen of chancroid patients.<sup>34</sup> These cytokines are secreted by CD4+ T lymphocytes.

A humoral response with production of IgG, IgM, and IgA occurs but does not confer lasting immunity. Many antigens, including the major outer membrane protein (MOMP) with a molecular weight of 40 KDa, have been characterized and the cell wall bears pili. The exact role of the various cytotoxins and hemolysins in pathogenesis is not clear, though they are thought to participate in tissue damage and ulcer formation. The virulence factors associated with *H. ducreyi* are likely to be the lipooligosaccharide (LOS), pili, extracellular toxins, and hemolysins.<sup>33,35–37</sup>

Chancroidal lymphadenitis is predominantly a pyogenic inflammatory response, with an unknown pathogenesis; the paucity of organisms in the bubo pus is also unexplained. Virulence determinants in the organism include superoxide dismutase enzymes and hemolysin. Superoxide dismutase enzymes are thought to increase the survival and persistence of the pathogenic organism within the host, whereas hemolysin contributes to ulcer formation and the invasion of epithelial cells.<sup>35</sup> The latter has immunogenic properties and is expressed both *in vitro* and *in vivo* by all known clinical strains of *H. ducreyi*. These properties make hemolysin a possible candidate for vaccine development.<sup>38</sup>

## Clinical Features

The incubation period is usually short and varies from 3 to 7 days, except in patients with concomitant HIV infection where it can be longer. The lesion may occur within 48 hours, if there are abrasions present over the genitalia at the time of intercourse. An erythematous papule appears at the site of entry of the organisms, which turns into a pustule, undergoes central necrosis and forms a characteristic, small, necrotic, tender, bleeding, nonindurated ulcer with ragged or undermined edges (Fig. 42.1). Autoinoculation may result in the formation of kissing ulcers or multiple ulcers in proximity to the primary ulcer (Fig. 42.2).

Men usually present with painful genital ulcer(s) and/or a painful inguinal mass, and at times, phimosis or paraphimosis. There is no prodromal phase. Rarely, the patient may present with purulent urethritis if the ulcer is located in the urethra.<sup>39</sup> Genital lesions in women may be asymptomatic or may present with mild vaginal discharge, dyspareunia, pain on voiding, or defecation. Skin rash or systemic reactions are not encountered. The typical lesion of chancroid is a nonindurated (soft sore), painful ulcer with ragged or undermined edges and a necrotic base covered with purulent exudate. It bleeds easily on touch. Distinctively, the



**Fig. 42.1:** Irregular, necrotic ulcer with ragged margins surrounded by an inflammatory margin over the urethral meatus is seen.



**Fig. 42.2:** Multiple, small, necrotic ulcers with ragged borders over the penile shaft and kissing chancroidal ulcer over the coronal sulcus are seen.

ulcer is variably painful depending upon the site of inoculation. The pain is more in men than in women. The ulcers are often multiple, however, not uncommonly, a solitary ulcer can occur. *H. ducreyi* seems to have a predilection for the stratified squamous epithelium, the mucosa being rarely affected. Ulcers in men usually occur over the preputial orifice, inner prepuce, frenulum, coronal sulcus, penile shaft, and anal orifice. The common sites affected in women are the labia, clitoris, fourchette, vestibule, anal margin, and cervix. Due to autoinoculation, the lesions may later spread to the peri-inguinale region, mons pubis, abdomen, and thighs. The rare occurrence of extragenital lesions over the fingers, tongue, lips, breasts, oral mucosa, and perianal area has been reported.<sup>33</sup>

Various clinical patterns of genital ulcers in chancroid have been described.<sup>40–44</sup> *Dwarf chancroid* consists of single or multiple herpetiform ulcers with or without associated inguinal lymphadenopathy. *Giant chancroid*, initially a small ulcer, extends rapidly to form a solitary destructive lesion (Fig. 42.3). This form is often associated with an inguinal bubo. In *transient chancroid*, the initial lesion resolves rapidly within 4–6 days, only to be followed by acute inguinal lymphadenitis with suppuration in 10



**Fig. 42.3:** Giant chancroid over the glans penis showing necrotic ulcer surrounded by erythematous borders.

to 20 days. *Follicular chancroid* originates in the pilar apparatus, and therefore occurs on hair-bearing areas. *Phagedenic chancroid* is characterized by widespread necrosis with deep and often extensive destruction of the genitalia (Fig. 42.4). *Pseudogranuloma inguinale* is a variant of chancroid that bears close resemblance to granuloma inguinale.<sup>43</sup> In *serpiginous chancroid*, multiple ulcers coalesce to form a serpiginous pattern. In *mixed chancroid*, nonindurated, tender ulcers occur along with an indurated, nontender ulcer of syphilis. *Chancroidal ulcer* is usually a tender, nonindurated, single large ulcer with the conspicuous absence of lymphadenopathy, and is caused by organisms other than *H. ducreyi*.



**Fig. 42.4:** Phagedenic ulcer with edema of penile shaft.



## BUBO

Subsequent to appearance of a genital ulcer, the regional lymph nodes become tender and inflamed. Lymphadenopathy occurs in 30–60% of patients (both in men and women), usually 1–2 weeks after the appearance of the genital ulcers. It is unilateral in two-thirds of the patients. The typical bubo consists of inguinal lymph nodes that have become fused and matted together by an acute inflammatory process of periadenitis forming a unilocular swelling with erythematous overlying skin. The swelling is painful and causes difficulty in walking. The bubo softens and undergoes suppuration to form unilocular fluctuant swelling (Fig. 42.5), which may rupture spontaneously resulting in ulceration. The margins of the opening (ostium) are necrotic and inflammatory. In about half of the patients, the inguinal lymphadenitis may subside without suppuration. In contrast to the transient nature of the primary lesion seen in lymphogranuloma venereum (LGV), the genital ulcers in chancroid may persist when the patient presents with inguinal bubo.<sup>45</sup> Features that differentiate the bubo of chancroid from that of LGV are summarized in Table 42.1.



**Fig. 42.5:** Chancroid ulcer over the penile shaft and an inflamed bubo in the left inguinal area.

**Table 42.1:** Differentiating Features of Lymphadenopathy in Chancroid and LGV

Features	Chancroid	LGV
Frequency of involvement	30–60%	~100%
Incubation period (bubo)	7–14 days	10–30 days
Unilateral	75%	66.7%
Primary genital ulcer (when patient presents with bubo)	Present	Absent
Sinus formation from rupture of bubo	Single	Multiple
Constitutional symptoms	–	+
Systemic spread	–	+
Groove sign	–	+ (20% cases)
Loculation	Unilocular	Multilocular

## Clinical Course and Complications

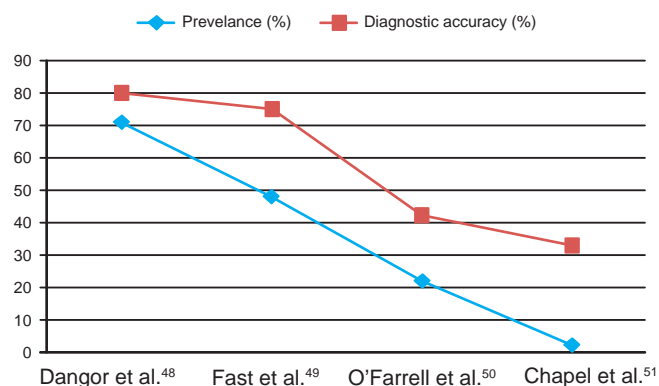
Chancroid is a self-limiting disease presenting with no serious problems in the majority of cases. Pain is the most important complaint. The primary lesions heal gradually or may spread locally through autoinoculation. Inguinal lymphadenitis may be minimal and subside gradually or progress to form a bubo that may rupture leaving behind large ulcerations. Complications occur more frequently in men that include balanitis, phimosis, paraphimosis, and the partial loss of tissue over the glans penis in phagedenic ulcers due to superinfection with anaerobic organisms. Discharging sinuses and large areas of ulceration at the site of the inguinal bubo may result in scar formation. Systemic infection or metastatic spread to distant sites has not been reported.<sup>46</sup> However, mild constitutional symptoms may occur due to secondary infection of the ulcers.

## Laboratory Diagnosis

The laboratory confirmation of chancroid is essential for accurate diagnosis, management, and epidemiological monitoring. In suspected cases of chancroid, testing for herpes simplex virus and syphilis should also be performed. It is interesting that the accuracy of the clinical diagnosis of chancroid is greatly affected by the prevalence of the disease.<sup>47</sup> A comparison of studies that evaluated the accuracy of a clinical diagnosis of chancroid (Fig. 42.6) suggests that the diagnostic accuracy decreases with the prevalence of the infection declining in the given population.<sup>48–51</sup> Therefore, with a continuous decline in the prevalence of the disease, the reliability of clinical diagnosis diminishes and laboratory confirmation becomes essential.

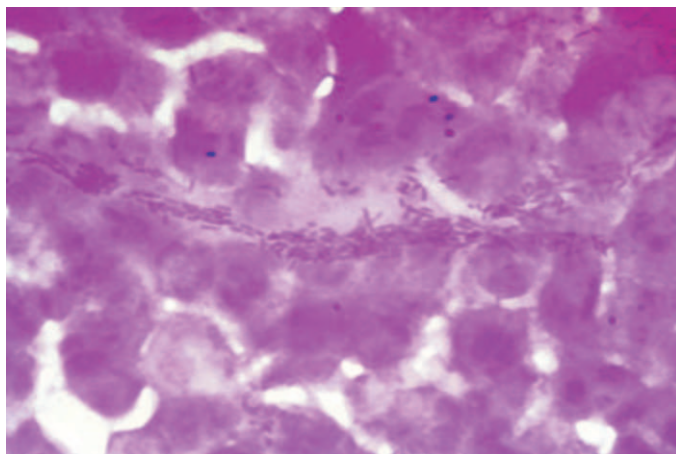
## MICROSCOPIC EXAMINATION OF THE SMEARS

The ulcer is cleaned with saline and exudate from the undermined edge of the lesion is obtained by rolling a cotton or calcium alginate swab. This is then smeared onto a glass slide and stained



**Fig. 42.6:** Accuracy of clinical diagnosis of chancroid (in men) in relation to prevalence in various studies. Note, a consistent decline in the clinical diagnostic accuracy with a decline in the prevalence of chancroid among patients with genital ulcer disease.





**Fig. 42.7:** Smear from chancroid ulcer showing typical 'school of fish' appearance. Courtesy: SJ Wineslaus and JB Schofield, UK. Reproduced with permission from: Schofield JB, Wineslaus SJ. Anorectal manifestations of sexually transmitted infections. *Colorect Dis* 2001;3:74–81.

with Gram, Unna-Pappenheim, Wright or Giemsa stains. The presence of typical streptobacilli lying in clusters, either inside the leukocytes or outside in chains, paralleling the shreds of mucus with the appearance of "schools of fish," "railroad tracks," and "fingerprints" may suggest a diagnosis of chancroid (Fig. 42.7). Often, it is difficult to demonstrate *H. ducreyi* in smears due to the polymicrobial flora of genital ulcers, which may resemble the *Ducreyi* bacillus. The organisms are less frequently demonstrated in the pus aspirated from a bubo, and culture from bubo is mostly sterile unless it has ruptured.<sup>3,52</sup> Some experts believe that direct microscopy of the smear is not reliable and should not be used in the routine diagnosis of chancroid.<sup>31</sup> It is of limited value because of low sensitivity (5–63%) and specificity (51–99%).<sup>53</sup>

### CULTURE AND IDENTIFICATION

Although *H. ducreyi* is a fastidious microorganism which is difficult to isolate from genital ulcer specimens, culture remains the main diagnostic tool, and for many years has been the "gold standard" for evaluating newer methods of diagnosis. However, even with the optimal combination of media, it is only about 80% sensitive. The specimen of choice is a swab that has been taken from the base of the genital ulcer.<sup>53</sup>

### Collection and Transport of Specimens

As *H. ducreyi* is a fastidious organism, it is essential that the specimens obtained from the base of ulcers or aspirate from the bubo should either be plated out directly onto the culture medium or sent to the microbiology laboratory rapidly (within 4 hours). The specimen should be obtained with a calcium alginate or plastic swab from the base of the ulcer after cleaning it with dry gauze. No selective transport medium is available, although Dangor et al. were able to grow relatively viable *H. ducreyi* for up to 4 days, from the specimens

stored at 4°C in a thioglycolate-hemin based medium containing L-glutamine and bovine albumin.<sup>48</sup> In swabs, *H. ducreyi* can survive for 2–4 hours only, and hence an alternative method (though less desirable) is to take the swab sample and place it in a transport media such as Amies.<sup>52–54</sup> Culture from intact buboes has even lower detection rates compared with culture from the ulcer base or culture from ruptured buboes.

### Culture Procedure

*H. ducreyi* grows best at 33°C in a microaerophilic, water saturated atmosphere containing 5% carbon dioxide, or in a traditional candle jar. Lenglet has been credited with the first successful *in vitro* culture of *H. ducreyi* in 1898.<sup>55</sup> Teague and Debert described the successful culture of *H. ducreyi* using fresh clotted rabbit blood heated to 55°C.<sup>56</sup> Numerous selective artificial media have been developed since. To date, the most widely used media are the gonococcal agar base enriched with 1% hemoglobin, 1% IsoVitalX, and 5% foetal calf serum; Mueller-Hinton agar enriched with 5% horse blood and 1% IsoVitalX; Columbia agar base with 5% lyzed horse blood, 2.5% yeast dialysate, and 1% IsoVitalX; enriched protease peptone agar; and heart infusion agar enriched with 10% foetal calf serum.<sup>34</sup> Nsanze et al. evaluated the potential benefit of using more than one medium to isolate *H. ducreyi* from clinical chancroid cases.<sup>57</sup> A simple inexpensive medium containing gonococcal agar base supplemented with 5% foetal calf serum and noncoagulated horse blood, and also a medium containing 0.2% activated charcoal instead of foetal calf serum, have been recommended for use in resource poor countries.<sup>58,59</sup> The success rate of *H. ducreyi* isolation in different culture media has been reported to range between 2% and 100%.

Cultures are incubated for 48 hours before noting the initial reading and kept for 5 days before reporting them negative. *H. ducreyi* exhibits an unusual tendency to autoagglutinate, when grown in a liquid medium or forms a cohesive colonial structure on agar plates. The colonies appear as nonmucoid, raised and granular, having a grayish-yellow color and can be pushed intact, across the surface of the agar with a bacteriologic loop. Gram staining of smears prepared from the colonies show gram-negative coccobacilli in short chains, clumps or whorls with individual bacterium showing bipolar staining. Identification can be done by  $\beta$ -lactamase production, oxidase test, nitrate reduction, requirement for hemin (X factor), and negative catalase, indole and urease tests.

### POLYMERASE CHAIN REACTION

Polymerase chain reaction (PCR) techniques have been developed to improve the sensitivity of diagnosis by DNA amplification<sup>60–66</sup> using primers based on the *H. ducreyi* 16S rRNA gene,<sup>60,63,65</sup> the *rrs* (16S)-*rrl* (23S) ribosomal intergenic spacer region,<sup>65</sup> an anonymous fragment of cloned *H. ducreyi* DNA,<sup>61</sup> the *groEL* gene,<sup>62</sup> or the 27 kDa *H. ducreyi*-specific protein (p27).<sup>66</sup> A multiplex PCR (M-PCR) assay has also been developed for the simultaneous amplification of DNA targets from *H. ducreyi*,

*Treponema pallidum*, and HSV types 1 and 2, and appears more sensitive than the standard diagnostic tests for the detection of these etiological agents in genital ulcer specimens.<sup>64</sup> Although PCR assays perform well with samples prepared from *H. ducreyi* cultures, they appear to be less sensitive when used to test genital ulcer specimens owing to the presence of Taq polymerase inhibitors in the DNA preparations extracted from the specimen.<sup>61</sup>

### ANTIGEN DETECTION BY IMMUNOFLUORESCENCE

Monoclonal antibodies (MAbs) have been raised against the 29 kDa outer membrane protein (OMP)<sup>67</sup> for direct immunofluorescence, and the MAb MAHD 7 against *H. ducreyi* lipooligosaccharide (LOS) for indirect immunofluorescence assays.<sup>68</sup> This assay can detect purified *H. ducreyi* LOS at a level of 25 pg/mL and could detect as few as 1000 CFU of *in vitro* grown *H. ducreyi*. The IF test identifies over 90% of the culture positive samples in addition to some culture negative chancroid cases. This technique has been shown to have a sensitivity of 100% and a specificity of 74% in comparison with culture, and a sensitivity of 81% in comparison with the PCR assay.

The immunolimus assay combines the specificity of a MAb raised against *H. ducreyi* LOS, and the sensitivity of the chromogenic limulus amebocyte lysate test for endotoxin.<sup>69</sup>

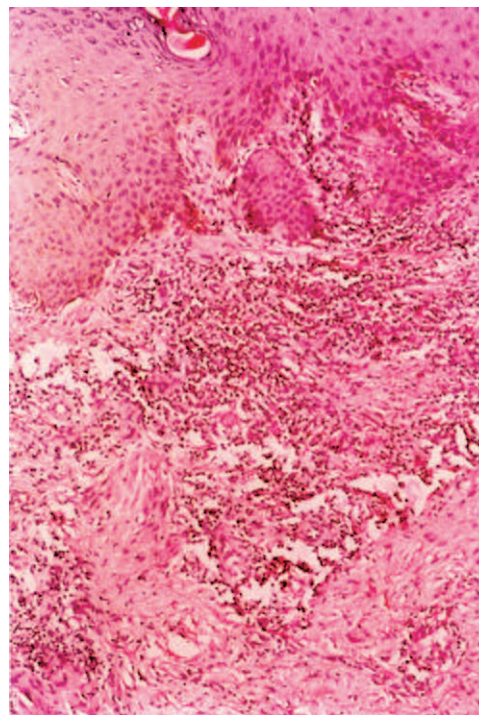
### ANTIBODY DETECTION BY SEROLOGICAL TESTS

Various serologic tests are available for the diagnosis of chancroid which include the enzyme immunoassays (EIAs), dot immunobinding, agglutination, complement fixation, and precipitation.<sup>70–72</sup> Antigens used for EIAs include the ultrasonicated whole cell antigen purified *H. ducreyi* LOS of OMPs.<sup>73</sup> None of these tests are commercially available at present. Though less sensitive to detect the circulating antibodies to *H. ducreyi* in individual patients having symptoms, these tests are helpful for screening in large scale epidemiological studies at the community level.<sup>74</sup>

Other tests include nucleic acid probe technology and mass spectrometric methods. *H. ducreyi* DNA can be detected by the technique of DNA-DNA hybridization using labeled *H. ducreyi*-derived probes. These probes are reliable and can detect 10<sup>4</sup> CFU of *H. ducreyi* in pure and mixed cultures. Also, oligonucleotides complementary to different regions in the 16S and 23S rRNA molecules of *H. ducreyi* have been synthesised.<sup>75</sup> Matrix assisted laser desorption-ionization time of flight mass spectrometry (MALDI-TOF MS) has been used for the rapid identification and speciation of *Haemophilus*.<sup>76</sup>

### HISTOPATHOLOGICAL EXAMINATION

The histological examination of the ulcer may be helpful in arriving at a diagnosis, even though the changes observed are not pathognomonic. The histopathologic picture consists of three zones: the *surface zone* at the floor is narrow and consists of neutrophils, fibrin, erythrocytes, and necrotic tissues; the



**Fig. 42.8:** Histology of chancroid ulcer showing dense infiltrate composed of mononuclear lymphocytes and plasma cells (H&E). Courtesy: Uma Nahar and Bishan D. Radotra, Chandigarh, India.

*middle zone* is wide, containing newly formed blood vessels showing marked proliferation of endothelial cells, thrombosis, and degenerative changes in the walls of the vessels; and the *deep zone* is composed of a dense infiltrate of plasma cells and lymphoid cells (Fig. 42.8).<sup>77</sup> Histological examination is useful to exclude malignancy in nonhealing or atypical ulcers.

### Differential Diagnosis

Chancroid has to be differentiated from other sexually transmitted GUDs, i.e., primary syphilis, genital herpes, granuloma inguinale, LGV and candidal balanitis, and non-STIs, such as traumatic ulcers, fixed drug eruption, and carcinoma. Coinfection of chancroid with *T. pallidum* or HSV may occur in up to 10% of patients.

### Antimicrobial Susceptibility

Recent reports from different parts of the world have revealed that clinically relevant antimicrobial resistance in chancroid has become common and is spreading rapidly.<sup>78–81</sup> More alarmingly, plasmid-mediated drug resistant strains of *H. ducreyi* to ampicillin, sulfonamides, chloramphenicol, tetracycline, streptomycin, and kanamycin have been reported.<sup>34</sup> However, these strains are extremely sensitive to several other antibiotics, especially the macrolides (erythromycin and azithromycin), the quinolones (ciprofloxacin and fleroxacin), and the third-generation cephalosporins (ceftriaxone, cefotaxime, and cefixime).<sup>33</sup>

## Treatment

Chancroid is an important cofactor in facilitating the transmission of HIV infection.<sup>1</sup> Prompt and adequate therapy of affected patients and their contacts is vital, in addition to the aggressive implementation of appropriate control and prevention measures for eradicating the disease.

Earlier treatments, such as sulfonamides, ampicillin, tetracyclines, and streptomycin, are no longer being recommended because of poor response rates and widespread resistance developed by *H. ducreyi* to these antimicrobials. Trimethoprim-sulfamethoxazole has been used extensively for chancroid in the past; however, resistance to this drug has now been noted in many parts of the world (Thailand, Kenya, and Rwanda). Erythromycin is effective in a dose of 500 mg 4 times a day, orally for 7 days.<sup>82</sup> Studies indicate that single-dose treatment with spectinomycin or ceftriaxone are also quite effective in the treatment of chancroid.<sup>80,83</sup> Azithromycin 1 g single-dose is highly effective but quite expensive. Fluoroquinolones, especially ciprofloxacin 500 mg given as single-dose orally has been found to be safe, convenient, and effective in chancroid; however, treatment failures have occurred in patients with concomitant HIV infection.

Current therapies recommended for chancroid are summarized in Table 42.2, and the treatment guidelines can be accessed at:

1. WHO: <http://apps.who.int/medicinedocs/en/d/Jh2942e/4.5.html#Jh2942e.4.5>

2. CDC: <http://www.cdc.gov/std/treatment/2006/genital-ulcers.htm#genulc2>
3. CEG/BASHH: <http://www.bashh.org/guidelines>

## SPECIAL CONSIDERATIONS

The safety of azithromycin in pregnant and lactating women has not been established. Ciprofloxacin is contraindicated in pregnancy, lactating women, children, and adolescents less than 18 years of age, hence erythromycin or ceftriaxone regimens should be used. No adverse effects of chancroid on pregnancy outcome or on the foetus have been reported. If associated with HIV infection, the patients have to be closely monitored. Healing of ulcers may be slower among HIV infected people and treatment failures have been reported with azithromycin, ceftriaxone, single-dose fleroxacin, low-dose erythromycin or ciprofloxacin. However, some recent studies have not shown any increased treatment failures in HIV-positive cases with low-dose erythromycin and single-dose ciprofloxacin. Currently, the data on therapeutic efficacy with the recommended ceftriaxone and azithromycin regimens among patients infected with HIV is limited. Hence, CDC recommends that these regimens should be used among persons known to be infected with HIV, only if a proper follow-up can be assured. However, some experts advocate the use of full doses of erythromycin for 7 days for treating HIV-infected persons.

**Table 42.2:** Comparative Analysis of the Current *Standard* Therapies Recommended for Chancroid by the World Health Organization (WHO 2003), the National Aids Control Organization (NACO, India 2005), the Centers for Disease Control (CDC, USA 2006), and the BASHH Clinical Effectiveness Group (CEG, UK 2007)

Drug	Dose	Dosing interval	Duration	Route	Recommending organization			
Erythromycin base	500 mg	QID	7 days	Oral	WHO	NACO	-	CEG
Erythromycin base	500 mg	TID	7 days	Oral	-	-	CDC	-
Erythromycin stearate	500 mg	QID	7 days	Oral	-	NACO	-	-
Erythromycin ethyl succinate	800 mg	QID	7 days	Oral	-	NACO	-	-
Azithromycin	1 g	Single-dose	-	Oral	WHO	NACO	CDC	CEG
Ceftriaxone	250 mg	Single-dose	-	Intra-muscular	-	NACO	CDC	CEG
Ciprofloxacin	500 mg	BD	3 days	Oral	WHO	-	CDC	CEG
Ciprofloxacin	500 mg	BD	3–5 days	Oral	-	NACO	-	-
Ciprofloxacin	500 mg	Single-dose	-	Oral	-	-	-	CEG
Doxycycline	100 mg	BD	7 days	Oral	-	NACO	-	-
Trimethoprim-Sulfamethoxazole	TMP (80 mg)-SMX (400 mg)	2 tabs BD	2 weeks	Oral	-	NACO	-	-



Although not yet commercialized for human use, a promising potential vaccine technology has been developed. In this scenario, high-risk individuals in endemic areas could undergo vaccination against a heme-receptor essential for *H. ducreyi* survival in skin. Antibodies arising after this vaccination have prevented infection *in vivo* in a porcine model of chancroid.<sup>84</sup>

## MANAGEMENT OF ULCERS AND FLUCTUANT BUBOES

Bed rest is recommended early in the course of disease because of pain. Local antiseptics are contraindicated as they would interfere with the diagnosis of concomitant syphilis by dark-ground microscopy. Local cleansing with normal saline is advocated. Fluctuant buboes can be aspirated with a needle from the adjacent healthy skin, and should not normally be incised as there is a risk of autoinoculation. Although incision and drainage of fluctuant buboes under antibiotic cover has been recommended in the past,<sup>82</sup> it is contraindicated according to the latest recommendations from WHO.

## FOLLOW-UP

Re-examination of the patient should be carried out on the seventh day after initiation of therapy. With the administration of proper treatment, the ulcers should show improvement symptomatically in 3 days followed by substantial re-epithelialization after 7 days. The time required for complete healing is related to the size of the ulcer and possibly the HIV status of the individual; large ulcers may require more than 2 weeks. Also healing is slower for some uncircumcised men who have an ulcer under the foreskin. Resolution of lymphadenopathy is slower than that of the ulcer.

## TREATMENT FAILURE

Coinfections with *T. pallidum* or HSV may result in partial or no improvement. During the past decade, high-level, plasmid-mediated drug resistance to sulfonamides, penicillins, kanamycin, streptomycin, tetracycline, chloramphenicol, and trimethoprim has been observed in *H. ducreyi* isolates. The most suitable medium to determine minimum inhibitory concentrations (MIC) is the Mueller-Hinton agar enriched with 1% hemoglobin, 5% foetal calf serum, and 1% HD supplement. Alternatively, a gonococcal agar base can be used.<sup>34</sup> If drug resistance is suspected, it is important to do antimicrobial drug susceptibility testing of *H. ducreyi* by the agar dilution technique<sup>85</sup> or the equally effective but simpler E-test.<sup>86</sup>

## MANAGEMENT OF SEXUAL PARTNER(S)

Sexual contacts within the last 10 days before the onset of patient's symptoms should be examined and treated, even in the absence of symptoms, in view of possible asymptomatic carriage.<sup>25</sup> Serological tests for syphilis and HIV should be offered to all patients and their contacts.

## Syndromic Approach

The clinical differentiation of chancroid from other GUDs is not reliable and culture of *H. ducreyi* is not routinely available, thereby imposing constraints on diagnosis, treatment, and control strategies.<sup>1</sup> Several studies have established that GUDs facilitate the risk of acquisition and transmission of HIV infection.<sup>87</sup> Hence, the current syndromic approach for the treatment of STIs, proposed by WHO is essential to manage GUDs and prevent HIV infection, especially in resource-poor nations where chancroid is endemic.<sup>88–91</sup>

## HIV and Chancroid

Chancroid facilitates the transmission of HIV by increasing both the infectiousness of HIV and the susceptibility to infection by the virus. Subjects with HIV infection and a concomitant chancroid ulcer demonstrate increased infectiousness through the following:

1. There is increased HIV shedding into the genital tract from ulcer exudates. In Cote d'Ivoire, HIV-positive female sex workers with cervicovaginal ulcers had higher rates of HIV isolation from cervicovaginal lavage fluids than those without ulcer disease (66.8% vs. 21%). Adjustment for the level of immunosuppression did not alter these findings. Treatment of the chancroid ulcer reduced HIV detection to levels similar to those of individuals without GUD.
2. Genital ulcers bleed during intercourse, resulting in potential increases in viral shedding and HIV infectiousness.
3. In men with GUD, there is increased concentration of the virus in seminal fluid, especially in those who also have nongonococcal urethritis. This is attributed to an increased plasma viral load from advanced disease or systemic immune activation by *H. ducreyi*.<sup>38</sup>

GUD, particularly chancroid, has been shown to increase the risk of acquiring HIV infection.<sup>17,92–94</sup> Genital ulcers provide a portal of entry for both HIV-1 and HIV-2. *H. ducreyi* infection recruits CD4+ lymphocytes and macrophages to genital surfaces and these cells are the principal early targets for HIV infection. Concomitant HIV infection may alter the clinical presentation of chancroid lesions. The ulcers may present with atypical features, such as large size and number, and extragenital location. The ulcers may take a longer time to heal. HIV appears to reduce the responsiveness of chancroid to standard therapy, especially single-dose regimens, possibly requiring treatment for a longer period and/or increased dosing.<sup>84</sup>

## Prevention and Control

*H. ducreyi* survives largely in networks with a high rate of sexual partner change, including MSM and CSWs. Control policies targeting these high risk groups will result in the rapid disappearance of chancroid from a community. Once endemic in Europe and North America, the incidence of chancroid declined steadily

early in the twentieth century. Greater awareness and changes in the pattern of commercial sex probably disrupted the conditions necessary to sustain chancroid as an endemic disease among these communities.<sup>1</sup> Several antibiotics, including some single-dose regimens, have the advantage of providing a rapid cure as well as ease of administration. Sporadic outbreaks can be controlled with effective treatment and preventive services targeted at high risk groups. More recently, the prevalence of chancroid has decreased in Thailand, Philippines, and Senegal with the implementation of intervention strategies targeting CSWs and their clients, a development that may contribute to the reduction of STIs and the stabilization of the HIV epidemic in these countries.

Greater awareness regarding diagnosis and treatment, strengthening diagnosis and treatment of STIs, widespread promotion of condom use, contact tracing, a targeted approach towards high risk groups, emphasis on maintaining local hygiene, and the use of a syndromic approach can all go a long way towards bringing down the incidence of this disease.

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## Introduction

Donovanosis is a progressive, mildly infectious bacterial infection that usually involves the genital area. The causative organism is a gram-negative bacillus, *Calymmatobacterium granulomatis*. A proposal that the organism be reclassified as *Klebsiella granulomatis* *comb nov* has been put forward.<sup>1</sup>

## History and Terminology

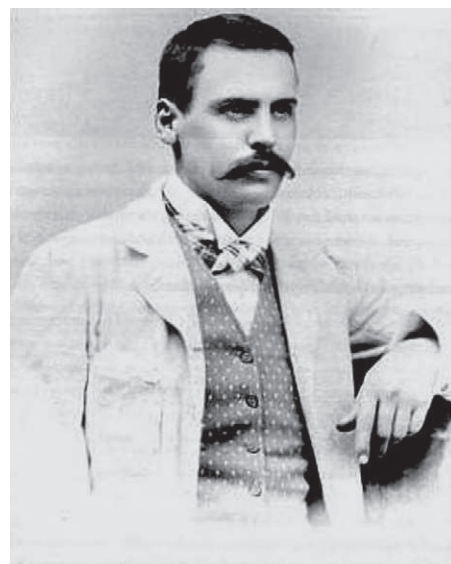
Donovanosis has been known under many different terminologies and this has undoubtedly led to confusion with lymphogranuloma venereum. The terms used most commonly are donovanosis and granuloma inguinale. This author, along with Marmell and Santora believes that donovanosis is the most appropriate term.<sup>2</sup>

Other terminologies used for donovanosis include the following:<sup>3</sup>

- Granuloma inguinale
- Granuloma venereum
- Lymphogranuloma inguinale
- Granuloma genito-inguinale
- Granuloma contagiosa
- Granuloma donovani
- Granuloma inguinale tropicum
- Ulcerating granuloma of the pudenda
- Infective granuloma
- Chronic venereal sores
- Ulcerating sclerosing granuloma
- Granuloma venereum genito-inguinale

Macleod, Professor of Surgery in Calcutta and originally from Scotland, first described donovanosis in 1882.<sup>4</sup> He reported cases of serpiginous ulceration in men and genital elephantiasis in a woman. Further cases were reported in British Guinea and the UK.<sup>5,6</sup>

The causative organism was first described by Charles Donovan in 1905.<sup>7</sup> Donovan (Fig. 43.1) was born in Calcutta, graduated from Cork University and the Royal University of Ireland and then entered the Indian Medical service.<sup>8</sup> While working in Madras, he identified the characteristic Donovan bodies measuring  $1.5 \times 0.7 \mu\text{m}$  in macrophages and epithelial cells of the stratum malpighii.



**Fig. 43.1:** Lieutenant-Colonel Charles Donovan.

Culture of the organism proved to be difficult. Aragao and Vianna claimed to have cultured the organism from ulcer lesions and identified it as *C. granulomatis*.<sup>9</sup> Further attempts at culture were unconvincing until 1943 when Anderson isolated the organism.<sup>10</sup> Earlier, Pund and Greenblatt described pathognomonic cells, the so-called Pund cells in 1937.<sup>11</sup> These consisted of large mononuclear cells 25–90  $\mu\text{m}$  in diameter filled with intracytoplasmic cysts with deep-stained bodies.

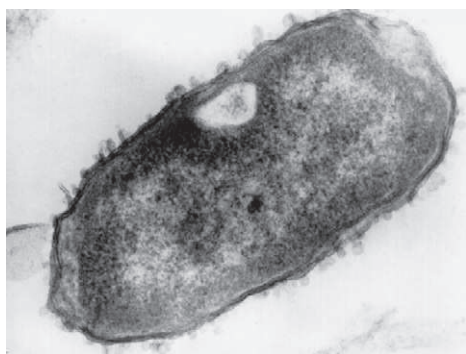
In 1951, Rajam and Rangiah, working in Madras, published a comprehensive WHO monograph based on their experience of having examined and treated nearly 2000 cases over 20 years.<sup>3</sup> From the mid 1960s, reports of the condition were limited until the late 1980s/early 1990s when the association between genital ulceration and HIV was identified and led to renewed interest in the condition. There followed increased efforts to tackle genital ulcers as a public health issue. In addition, syndromic management algorithms for genital ulcers were implemented more effectively along with the recommendation that cases be followed-up until

complete healing was achieved. Subsequently, the incidence of donovanosis decreased to the extent that cases are now almost sporadic even in areas where the condition was once prevalent in significant numbers.

## Biology

The causative organism is an intracellular, gram-negative pleomorphic bacterium identified as the Donovan body. Goldzieher and Peck<sup>12</sup> identified Donovan bodies in histological tissue sections in 1926 and described a large mononuclear cell containing the specific organisms. Pund and Greenblatt used Delafield hematoxylin and eosin and Dieterle silver impregnation methods to describe this characteristic cell filled with intracytoplasmic cysts that eventually rupture with the release of infective organisms.<sup>11</sup> Sehgal described gram-negative intra- and extra-cellular Donovan bodies with different morphologic features consisting of coccoid, coccobacillary, and bacillary forms.<sup>13</sup>

Electron microscopy studies have shown organisms with gram-negative morphology and a large capsule but no flagella (Fig. 43.2).<sup>14</sup> Filiform protrusions may be seen on a corrugated cell wall<sup>15</sup> but other surface structures are not found.<sup>16</sup> Early on, the causative organism was noted to possess marked similarities to *Klebsiella* species.<sup>17</sup> More recently, polymerase chain reaction (PCR) tests were developed in Darwin and Durban and further molecular characterization of the causative organism was undertaken.<sup>1,18–20</sup> DNA sequencing of the 16S rRNA and *phoE* genes demonstrated that *C. granulomatis* had a greater than 99% similarity with *K. pneumoniae* and *K. rhinoscleromatis*. Carter et al. proposed that the causative organism be reclassified as *K. granulomatis comb nov* and set out an amended description of the genus *Klebsiella* to include donovanosis.<sup>1</sup> However, Kharsany et al. performed a phylogenetic analysis of *C. granulomatis* based on 16S rRNA gene sequences and found that strains had similarities of only 95% and 94%, respectively, to the genera *Klebsiella* and *Enterobacter*.<sup>20</sup> They concluded that *C. granulomatis* was a unique species belonging to the subclass of *Proteobacteria* and distinct from other related organisms. Differences in these results have not been explained, and resolution of the conflict regarding classification has not yet been achieved.



**Fig. 43.2:** Electron microscopic picture of Donovan body. Courtesy: Mithilesh Chandra, Noida, India.

## Epidemiology

In the preantibiotic era donovanosis was prevalent in many diverse geographic locations. Rajam and Rangiah stated that the disease was distributed in both hemispheres and endemic in southern China, the East Indies, northern Australia, West and central Africa, some countries of Central, South, and North America, and the West Indies.<sup>3</sup> In the United States, Greenblatt estimated a population prevalence of 5,000–10,000 cases in 1947.<sup>21</sup> Nowadays significant numbers are found in only a few developing countries and these are decreasing year by year. Sporadic cases do occur in developed countries and are often the subject of case reports. A small epidemic of 20 cases was reported in 1984 in the US.<sup>22</sup>

The main foci of donovanosis in recent times have been in Papua New Guinea,<sup>23</sup> southern Africa, particularly the Durban-KwaZulu-Natal region,<sup>24</sup> and eastern Transvaal.<sup>25</sup> Elsewhere, significant numbers of cases have been reported from Zimbabwe<sup>26</sup>, parts of India,<sup>27</sup> northeast Brazil<sup>28</sup>, French Guyana,<sup>29</sup> and aboriginal communities in Australia.<sup>30</sup> Papua New Guinea seems to have been the worst affected region; in 1980 donovanosis accounted for 46% of genital ulcers in women.<sup>31</sup> In a study at five health centers in 1989/90, donovanosis was the second most common cause of genital ulceration after genital herpes<sup>32</sup> and the most common sexually transmitted infection (STI) among new STI attendees in Porgera Enga province in 1992/3.<sup>33</sup> However, a more recent WHO consensus report states that donovanosis has now become rare in Papua New Guinea.<sup>34</sup> The largest epidemic recorded was in Dutch South New Guinea between 1922 and 1952, when 10,000 cases were reported from a population of 15,000.<sup>35</sup>

In the main STI clinic in Durban, South Africa, following a decrease after a peak in 1969–74,<sup>23</sup> the numbers of donovanosis cases recorded in the annual reports of the medical officer increased from 312 in 1988 to 3153 in 1997.<sup>24,36</sup> In a microbiologic study of genital ulcer disease among STI clinic attenders in Durban, donovanosis was diagnosed in 11% of men<sup>37</sup> and 16% of women in 1988.<sup>38</sup> Although genital ulcer diagnoses in Durban were recorded syndromically without mention of likely specific etiologies after 1997, it would appear that donovanosis has now decreased significantly. Recent genital ulcer surveys in men identified donovanosis in 4% in 1999<sup>39</sup> with a further reduction to less than or equal to 1% in 2001<sup>40</sup> and 2004.<sup>41</sup> Prior to the 1980s, it was reported that few cases were present in South Africa and the suggestion made that donovanosis had all but disappeared.<sup>42</sup> A more likely explanation is that there were few individuals with any interest in STDs in South Africa at that time so that the condition attracted little interest and went unrecognized or was diagnosed as lymphogranuloma venereum.<sup>43</sup> Elsewhere in Africa sporadic cases of donovanosis have been reported in recent times from Botswana,<sup>44</sup> the Central African Republic<sup>45</sup> Gabon<sup>46</sup>, and Zambia.<sup>47</sup>

In India, donovanosis was prevalent mainly in the states of Madras and Orissa in the south and Himachal Pradesh in the north with the greatest incidence along the eastern seaboard.<sup>3</sup> Between 1993 and 1997<sup>48</sup> donovanosis accounted for 14%



of genital ulcer cases at a southern STI clinic, 15% of whom were HIV positive but in North India the number of cases dropped considerably in the 1990s<sup>49</sup>. In Jamaica, the prevalence of donovanosis diagnosed on clinical grounds decreased from 4.1% in 1982/3 to 2.3% in 1990/1.<sup>50</sup>

In Australia a donovanosis elimination program was launched in 1998 among Aborigines.<sup>51,52</sup> This involved designated clinical officers who coordinated clinical protocols, performed health-promotion activities, validated epidemiological data, ensured laboratory control, and assisted in the follow-up of hard to reach cases. This program has achieved remarkable success and reduced the number of annual cases to a handful throughout Australia.<sup>53</sup>

It has been questioned as to whether donovanosis is sexually transmitted because of the low incidence of the disease, the differences in the racial and sex distributions, uncertainty about the incubation period, infrequency of cases of conjugal infection, and the occurrence of primary extragenital lesions.<sup>54</sup> The condition undoubtedly has several unusual epidemiologic features that warrant further scrutiny.

The majority of cases are in the 20- to 40-year age group, that is, the most sexually active. Most case series have recorded a preponderance of males, although in some studies with limited numbers of cases, such as in Zambia,<sup>47</sup> western Australia,<sup>55</sup> and eastern Transvaal, South Africa,<sup>56</sup> more women than men have been reported. Rajam and Rangiah<sup>3</sup> recorded 1350 men and 562 women in their large series, and similar male-to-female ratios have been reported in Zimbabwe<sup>26</sup> and southeast India.<sup>57</sup> Higher male-to-female ratios of more than 6:1 have been reported from Papua New Guinea<sup>23</sup> and India.<sup>58</sup>

The incubation period is uncertain. Sehgal and Prasad<sup>59</sup> found the average incubation period to be 17 days, but a range of 1–360 days has been reported.<sup>60</sup> Experimental production of typical donovanosis lesions was induced in humans 50 days after inoculation.<sup>61</sup>

Among sexual partners of index cases, wide variations in the rates of infection have been reported. In Papua New Guinea<sup>23</sup> and the US<sup>62</sup> the coinfection rate was 1–2%, whereas in India rates of up to 50% were reported among marital partners examined.<sup>57,63</sup> A more recent study of 255 cases in India in which eight couples were examined found conjugal involvement in one pair only.<sup>64</sup> In many cases the disease is mild, particularly in men, and examination of all regular sexual partners is recommended.

Transmission via fecal contamination of abraded skin was suggested as a possible mode of transmission by Goldberg.<sup>65</sup> Although he isolated the causative organism from feces, there are no subsequent reports to support this hypothesis. Cases in children have been attributed to sitting on the laps of infected adults.<sup>66</sup> Disseminated donovanosis has been reported in a neonate born to a mother with a large granulomatous lesion of the vulva who incurred a third-degree tear during delivery.<sup>67</sup>

## Immunology

McIntosh first described antibody production against the organism and he achieved experimental transmission of the

organism from one individual to another.<sup>68</sup> Skin testing was tried but found to have poor sensitivity.<sup>69–71</sup>

No serologic tests are currently in generalized use. Complement-fixation tests were developed and found to be reasonably sensitive<sup>69–72</sup> but had a poor specificity. Positive immunofluorescence and immunoperoxidase reactions have been identified in tissue sections from donovanosis lesions after incubation with sera from patients with donovanosis.<sup>73</sup>

An indirect immunofluorescent technique using sections from proven donovanosis lesions as antigens had a high sensitivity for established lesions but was not deemed suitable for early donovanosis ulcers. However, this test could be of use as an epidemiologic tool in population studies.<sup>74</sup> A study of lymphocyte sub-populations showed an increase in B lymphocyte and immunoglobulin levels but no further work has been done in this area.<sup>75</sup> In Durban, HLA studies showed an association between donovanosis and HLA-B57 and a trend toward resistance to disease with HLA-A23.<sup>76</sup>

## Clinical Features

The first sign of infection is usually a firm papule or subcutaneous nodule that later ulcerates. Four types of donovanosis are described classically: (i) Ulcerogranulomatous—the most common variant—non-tender, fleshy, exuberant, single or multiple, beefy-red ulcers that bleed readily when touched (Figs. 43.3–43.5); lesions spread by direct extension and autoinoculation. (ii) Hypertrophic (Fig. 43.6) or verrucous type—an ulcer or growth with a raised, irregular edge, sometimes completely dry with a walnut-like appearance. (iii) Necrotic, usually a deep, foul-smelling ulcer causing tissue destruction. (iv) Sclerotic or cicatricial, characterized by extensive formation of fibrous and scar tissue; this variant usually requires histological examination to confirm the diagnosis.

The genitals are affected in 90% of cases and the inguinal region in 10%. The usual sites of infection are, in men, the prepuce, coronal sulcus, frenum, and glans penis and, in women, the labia minora and fourchette. A preponderance of cases has long been recognized in uncircumcised men.<sup>77</sup> Lesions of the cervix may mimic cervical carcinoma. Extragenital lesions occur



**Fig. 43.3:** Typical subpreputial ulcerogranulomatous donovanosis lesions.



Fig. 43.4: Penile donovanosis lesions.



Fig. 43.5: Confluent donovanosis lesions at fourchette.



Fig. 43.6: Inguinal hypertrophic lesions of donovanosis.

in 6% of cases but are often missed in non-endemic areas.<sup>3,78,79</sup> Sites of infection include the lip, gums, cheek, palate, pharynx, neck, nose, larynx, and chest. Extragenital lesions are usually associated with primary genital disease. On the rare occasions when primary extragenital lesions are diagnosed, the possibility of rhinoscleroma should be considered. Rhinoscleroma is caused by *K. rhinoscleromatis* and is an organism closely related to the causative organism of donovanosis.

Lymphadenitis is an uncommon finding.<sup>80</sup> Disseminated donovanosis is rare, but secondary spread to liver and bone may occur and is usually associated with pregnancy and cervical lesions. Polyarthrititis and osteomyelitis are rare complications.<sup>81</sup>

## Complications and Sequelae

Rajam and Rangiah found carcinoma, either as a complication of or a sequel to long-standing donovanosis, to be a rare occurrence, seen in 0.25% of 2000 cases.<sup>3</sup> Positive reactivity with *C. granulomatis* antigens was found in 9 of 62 cases of carcinoma of the penis in Jamaica, but this work was not developed further.<sup>82</sup>

Nowadays, the most frequent complication is pseudoelephantiasis, which is more common in women and found in up to 5% of cases.<sup>83</sup> Surgical intervention may be required for advanced intractable lesions.<sup>84</sup> Stenosis of the urethra, vagina, or anus may occur in the sclerotic variant of donovanosis.<sup>3</sup>

The differential diagnosis between donovanosis and squamous cell carcinoma of the penis may be difficult.

Donovanosis ulcers may be coinfecting with other STIs, particularly syphilis.<sup>31,37</sup> Such cases justify management by the syndromic approach with treatment for both conditions. However, it is important that these patients be followed, even when managed by primary healthcare workers, until complete healing is achieved. The presence of donovanosis ulcers does not preclude sexual intercourse,<sup>85</sup> and the risks of reinfection should be stressed at the initial consultation.

## Pregnancy and Donovanosis

Donovanosis has a more aggressive course during pregnancy and lesions may increase in size rapidly.<sup>77,86,87</sup> Neonatal cases may present with ear infections following transmission from an infected mother.<sup>88,89</sup> Children born to mothers with untreated donovanosis should receive antibiotic prophylaxis. Careful cleansing of neonates born to infected mothers is recommended.<sup>88</sup>

## Donovanosis and HIV

The classic STIs, and genital ulcer diseases in particular, are significant risk factors for HIV in developing countries. In Durban, in a population where HIV infection had been introduced only recently, the proportion of men with donovanosis and HIV infection increased significantly as the duration of lesions increased, thereby suggesting that HIV was acquired via sexual intercourse in the presence of ulcers.<sup>90</sup>

The treatment of donovanosis may need to be modified in HIV-infected patients with significant immunosuppression. In Mumbai, India, the mean healing time in HIV-positive patients with donovanosis was 25.7 days compared to 16.8 days in HIV-negative subjects.<sup>27</sup> In Brazil, two AIDS patients with donovanosis failed to respond to conventional treatment with combinations of cotrimoxazole, tetracycline, and thiamphenicol.<sup>91</sup> Interestingly, two HIV-positive patients with oropharyngeal infections with *K. rhinoscleromatis* required prolonged courses of antibiotics before clinical cure.<sup>92</sup> However, among HIV-positive pregnant women without significant documented immunosuppression, the clinical presentation and response to treatment in donovanosis appeared to be unaltered by HIV.<sup>93</sup> Further clarification of the role of oral azithromycin in the management of donovanosis in HIV-positive



patients is awaited. Other complications of donovanosis are uncommon in HIV-infected individuals, although one case of co-existent squamous cell carcinoma is reported.<sup>94</sup>

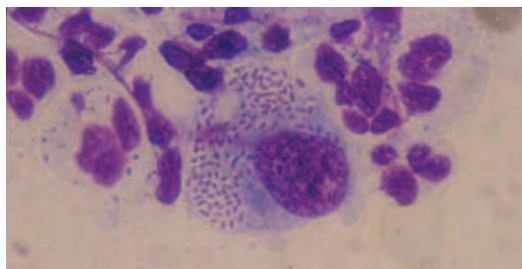
## Diagnosis

### DIFFERENTIAL DIAGNOSIS

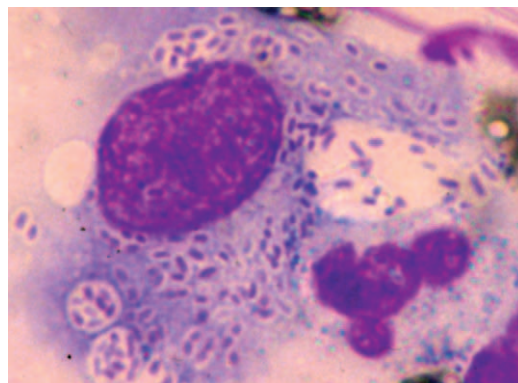
Ulcerogranulomatous donovanosis lesions have a characteristic appearance and should be distinguished readily from the other classic STI causes of genital ulcer disease.<sup>95</sup> However, primary syphilitic chancres, secondary syphilis (condylomata lata), chancroid, and large herpetic ulcers can all be mistaken for donovanosis. Amoebiasis and carcinoma of the penis should also be considered if tissue destruction or necrosis is present. In developed countries, a history of travel and sex in an endemic country may lead to a diagnosis of donovanosis.<sup>96</sup>

### TISSUE SMEARS

Direct microscopy of tissue smears is the mainstay method of diagnosis. Confirmatory specimens can usually be obtained as long as an adequate smear is prepared and antibiotic treatment has not been started. Most centers with experience with donovanosis have developed their own methods for maximizing the diagnostic yield from clinical specimens. Greenblatt and Barfield<sup>97</sup> advocated obtaining crush biopsy samples from the edges of lesions and stressed the importance of obtaining clean specimens for the preparation of tissue smears. Rajam and Rangiah<sup>3</sup> obtained material by means of a curette, forceps, the sharp end of a broken slide, or the edge of a safety razor blade and crushed the specimen between two slides and stained by the Leishman or Giemsa methods. Rapid results have been achieved using material obtained with a chalazion spoon.<sup>98</sup> Other stains used include Delafield hematoxylin and eosin,<sup>11</sup> Wright,<sup>99</sup> and pinacyanole.<sup>100</sup> A 100% success rate was claimed using a slow-Giemsa (overnight) technique.<sup>101</sup> A modified Giemsa stain (RapiDiff) has yielded rapid results in a busy clinic environment<sup>102</sup> (Figs. 43.7, 47.8). The organisms are pleomorphic and are usually ovoid or bean-shaped. The capsule is pink and the body of the organism is bluish/purple. Giemsa staining may show bipolar inclusions and often have a safety-pin appearance. Organisms stained with RapiDiff have a more homogeneous picture. Organisms may occur in clusters



**Fig. 43.7:** Tissue smear stained by rapid Giemsa (RapiDiff) technique showing numerous Donovan bodies in large monocyte (Pund cell).

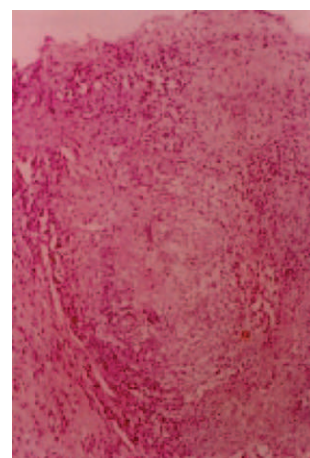


**Fig. 43.8:** Tissue smear stained by RapiDiff showing Donovan bodies in small cysts.

or in small cysts inside the mononuclear cell. Donovan bodies have also been identified in Papanicolaou smears.<sup>103</sup> If multiple swabs are taken from ulcers and donovanosis is considered likely, the smear for Donovan bodies should be taken first so that an adequate amount of material can be obtained from the ulcer.

### HISTOPATHOLOGY

Biopsy and histologic examination may be required for lesions that are small, dry, sclerotic, or necrotic. Giemsa or silver stains are the most effective methods for visualizing the organisms in tissue sections. The characteristic histologic picture shows chronic inflammation with infiltration of plasma cells and polymorphonuclear leukocytes (Fig. 43.9)<sup>12</sup>; the dermis shows a dense cellular infiltrate with large numbers of plasma or Pund cells. Ulceration and acanthosis with focal collections of polymorphonuclear leukocytes are found in the epidermis; elongation of rete ridges occurs in association with the hypertrophic variant.<sup>13</sup>



**Fig 43.9:** Histology of donovanosis showing ulcerated epidermis, pseudoepitheliomatous hyperplasia and dense infiltrate in dermis, primarily of plasma and mononuclear cells (H&E, x 550). *Courtesy:* Uma Nahar and Bishan D. Radotra, Chandigarh, India.



## CULTURE

After Aragao and Vianna's initial publication,<sup>9</sup> Cornwall and Peck cultured an organism that when injected into rabbits produced granulomatous lesions simulating donovanosis at the site of injection.<sup>104</sup> DeMonbreun and Goodpasture<sup>105</sup> grew gram-negative bacilli of the *Aerogenes* group from ulcers and feces of patients with donovanosis in a filtrate of chick membrane in both the capsulated and non-capsulated forms. Greenblatt et al.<sup>61</sup> were able to transmit the disease into human volunteers by introducing material from a pseudobubo but failed to grow the organism on the chorioallantois of chick embryos.<sup>106</sup>

Attempts at culture remained unconvincing until 1943 when Anderson<sup>10</sup> reported the isolation of the causative organism on the yolk sac of chick embryos and proposed a new genus, *Donovania*, and species, *granulomatis*.<sup>107</sup> Further efforts to develop an artificial medium for the culture of *D. granulomatis* met with only limited success. Some growth was achieved by Dunham and Rake using beef heart infusion agar and normal chick embryo yolk sacs with subsequent transfer to tryptose beef heart infusion broth and modified Levinthal stock broth.<sup>69</sup> Positive skin reactions were demonstrated in human subjects with donovanosis after injection of bacterial antigen prepared from infected yolk sacs.<sup>72</sup> It would now seem that some of the earlier claims of successful cultures may have been due to contamination.

After 1962,<sup>65</sup> there were no reports of successful culture until 1996/7 in Durban,<sup>108,109</sup> where the causative organism was shown to multiply in a monocyte co-culture system from biopsy specimens after pretreatment with amikacin. In Darwin, the organism was grown using a modified chlamydia culture system with human epithelial cell lines.<sup>110</sup>

## MOLECULAR METHODS

In Darwin amplification of Klebsiella-like sequences was achieved using primers targeting the *phoE* gene. A diagnostic PCR was produced using the observation that two unique base changes in the *phoE* gene eliminate HaeIII restriction sites enabling clear differentiation from closely related species of Klebsiella.<sup>18,19</sup> A colorimetric PCR detection system can now be used in routine diagnostic laboratories.<sup>111</sup> A genital ulcer multiplex PCR that includes *C. granulomatis* in addition to herpes simplex viruses, *Haemophilus ducreyi*, and *Treponema pallidum* has been developed.<sup>112</sup> The presence of *C. granulomatis* was confirmed by restriction enzyme digestion and nucleotide sequencing of the 16rRNA gene for phylogenetic analysis.

## Management

### MEDICAL TREATMENT

Donovanosis is one of the few bacterial infections that could be treated in the preantibiotic era. Antimony compounds were used successfully for primary infections but had limited efficacy for recurrences or reinfections.

The first antibiotic shown to be effective for donovanosis was streptomycin in 1947.<sup>113</sup> Nowadays, various therapeutic treatments are used and probably reflect local availability of different drugs. Streptomycin has been used extensively in India and is effective for large lesions, although daily injections are required.<sup>114</sup> Chloramphenicol has been used in Papua New Guinea,<sup>115</sup> cotrimoxazole in India<sup>116</sup> and South Africa,<sup>117</sup> and thiamphenicol in Brazil.<sup>118</sup> Healing is usually achieved with tetracycline, although resistance is reported.<sup>119</sup> Norfloxacin,<sup>120</sup> ciprofloxacin,<sup>121</sup> and high-dose ceftriaxone<sup>122</sup> are also effective. Gentamicin 1 mg/kg three times daily intramuscularly or intravenously can be given if there is no response in the first few days with other regimens. Erythromycin is recommended during pregnancy. Encouraging results have been shown with azithromycin which has now become the drug of choice; a course of 500 mg daily for 1 week or 1 gram weekly for 4–6 weeks are both effective<sup>123</sup>; WHO recommends 1 gram followed by 500 mg daily,<sup>124</sup> and the Centers for Disease Control and Prevention recommends 1 gram weekly for at least three weeks until lesions are healed.<sup>125</sup> Expanded access to azithromycin would be a major step forward and contribute significantly to limiting compliance problems with other therapies currently in use.

Children with donovanosis should receive a short course of azithromycin 20 mg/kg. Children born to mothers with untreated donovanosis should receive prophylaxis with a three-day course of azithromycin 20 mg/kg once daily.<sup>88</sup>

## INFORMATION, EDUCATION, AND COUNSELING

Poor understanding has in the past led patients with severe donovanosis to become shunned and ostracised.<sup>3</sup> Many sufferers express profound feelings of shame, guilt, and embarrassment. Some have resorted to suicide. Even now, extreme rejection is not unusual.<sup>126</sup>

In many developing countries, donovanosis patients are seen at STI clinics after attending primary healthcare centers where various treatment approaches have failed. Patients with large lesions of donovanosis may need prolonged courses of antibiotics and require careful explanation and reassurance about a condition that they may have had for a long time. Where possible, this is probably best given by staff that have chosen to work with STI patients and can give individual attention coupled with a sympathetic, non-judgmental approach.<sup>127</sup> Clearly, there is a need for on-going education of healthcare workers about donovanosis in endemic areas and to raise community awareness of the importance of genital ulcer disease as a proven risk factor for HIV transmission.<sup>128</sup>

## Prevention and Control

Donovanosis is one of the most easily recognizable causes of genital ulcer disease clinically in endemic areas.<sup>95</sup> Because it is limited to a few specific geographic locations, local elimination and even global eradication are realistic objectives<sup>53,129</sup> that are justified if the high proportion of HIV transmissions attributable to genital ulcers is taken into consideration.<sup>130</sup> Such programs would need to appreciate the diverse nature of the communities affected and include careful appraisal of local customs and beliefs.

Although communities in the donovanosis-endemic countries of Papua New Guinea, India, South Africa, Brazil, and Australia differ markedly, they all have similarities that may be relevant to donovanosis control. Most individuals with donovanosis in these communities are subject to social deprivation, low socioeconomic status, and poor standards of personal genital hygiene.

Donovanosis should remain high on the list of differential diagnoses of genital ulceration in female sex workers in donovanosis-endemic countries. In India,<sup>3</sup> USA,<sup>22</sup> and Papua New Guinea,<sup>23</sup> prostitutes have been identified as source contacts of index cases and usually have clinically detectable lesions. In Papua New Guinea, local sexual practices and beliefs may play a significant role in the spread of donovanosis: It is not unknown for many men to have sexual intercourse with a single woman during festival occasions<sup>131</sup>; furthermore, some men believe that impurities in their blood cause donovanosis ulcers and resort to self-mutilation in an attempt to “release” the cause of the problem.<sup>132</sup> It should also be noted that Papua New Guinea has the highest prevalence of HIV in the Oceania region.<sup>133</sup>

Since the overall prevalence of donovanosis in most endemic areas is low, mass surveys to identify cases or mass treatment campaigns are not justified. However, mass treatment of cases identified in house-to-house visits in Goilala, Papua New Guinea, was successful in controlling a localized epidemic in the 1950s.<sup>66</sup>

Global eradication of donovanosis remains a possibility but will require significant input and leadership from the WHO if it is to be placed on the disease-eradication agenda.

### Summary

Donovanosis is a cause of genital ulceration found mainly in a limited number of developing countries. Sporadic case may occur elsewhere. The causative organism is *Calymmatobacterium granulomatis* although a proposal has been put forward to reclassify it as *Klebsiella granulomatis*. The classical ulcerogranulomatous lesion is a beefy, red ulcer that bleeds readily to the touch. Other types include hypertrophic, necrotic and sclerotic variants. The genitals are affected in 90% of patients and the inguinal region in 10%. Extragenital lesions may involve the lip, gums, cheek, palate, pharynx, larynx and chest. The diagnosis is usually confirmed by microscopic identification of Donovan bodies in tissue smears. Donovan bodies can be seen in large, mononuclear cells as Gram-negative, intracytoplasmic cysts filled with deeply staining bodies that may have a safety-pin appearance. Histological changes include chronic inflammation with infiltration of plasma cells and neutrophils. A genital ulcer multiplex PCR that includes *C. granulomatis* has been developed. Azithromycin is the drug of choice. Improved STI control focusing on genital ulcers in the wake of the HIV epidemic has resulted in a significant decrease in the global burden of donovanosis.

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# Bacterial Vaginosis

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## Definition

Bacterial vaginosis (BV) is the most common form of vaginal infection in women of reproductive age. It is characterized by a replacement of the normal lactobacillus flora with an overgrowth of anaerobic/facultative bacteria, associated with a rise in pH above 4.5. It was formerly known as non-specific vaginitis, Haemophilus, Corynebacterium, or Gardnerella vaginitis, non-specific vaginosis, or anaerobic vaginosis; BV has not been linked to infections outside the vagina.

## History (Taxonomic Controversy)

Before 1955, leukorrhea and “non-specific vaginitis” were the terms most frequently used to describe BV. It was thought that mixed bacterial infections accounted for many otherwise unexplained vaginal discharges, even though the putative etiological agents could not be differentiated from bacterial organisms commonly inhabiting the vagina. Such cases were often classified as non-specific vaginitis, or vaginitis unrelated to *Trichomonas vaginalis* or *Candida albicans*,<sup>1</sup> despite the fact that no clearly defined clinical pattern for such disease has ever been delineated.

The concept of non-specific vaginitis was discredited by Gardner and Dukes in 1955. They provided the first clear evidence that *H. vaginalis* is associated with the vast majority of these cases.<sup>2</sup> The name *H. vaginalis* was widely accepted until 1961 when LaPage demonstrated that it had neither X nor V factors, which were characteristics of *Haemophilus species*. He suggested that *H. vaginalis* might belong to the genus *Corynebacterium*.<sup>3</sup> In 1963, Zinnemann et al. concluded that *H. vaginalis* was a gram-positive *Corynebacterium*, and proposed the name *Corynebacterium vaginale*,<sup>4</sup> which was endorsed by Dunkelberg et al. in 1969.<sup>5</sup> In the 1970s the proposed name was used despite the accumulating evidence that the organism was not a *Corynebacterium*<sup>6,7</sup> and Park and associates were of the opinion that there was no precisely appropriate genus designation for this organism.<sup>8</sup> In 1980, Greenwood et al. suggested the name *Gardnerella vaginalis* to establish a new genus; this was supported by Piot and colleagues.<sup>9,10</sup> Some clinicians use the

term *Gardnerella vaginalis* vaginitis or BV, whereas others use the term “anaerobic vaginosis.”<sup>11</sup> BV is associated with vaginal overgrowth not only of anaerobic bacteria, but also of certain species of facultative bacteria and genital mycoplasmas.<sup>12,13</sup> The term “vaginal bacteriosis” was proposed by Huth to emphasize an increase in vaginal bacteria.<sup>14</sup> Garrison encouraged the use of the term “bacterial vaginopathy,” retaining the abbreviation “BV.” The reason is that the suffix “osis” is applied to Greek stems only and should not be used with the Latin stem “vagin.”<sup>15</sup> However, the term bacterial vaginosis is still most commonly used to identify this syndrome.

## Epidemiology

BV is the most common abnormal vaginal condition and is the leading cause of abnormal vaginal discharge (AVD) accounting for up to 48% of the cases.<sup>16–18</sup> The reported prevalence of BV is dependent on varying diagnostic criteria. Gram stained scoring systems generally report higher rates of BV than those using Amsel criteria.

In various populations across the world 9–50.9% of sexually active asymptomatic women,<sup>19–24</sup> and 4.9–52% of pregnant women have laboratory indicators of BV.<sup>25–29</sup> Generally, higher rates are found in developing countries than industrialized ones, with black women appearing to have double the rates of white. Among adolescents, rates of 13–31.9% have been reported.<sup>30,31</sup> In four studies there was no significant difference in the prevalence of BV or *G. vaginalis* between the sexually active and virginal groups supporting the conclusion that BV is not an exclusively sexually transmitted disease.<sup>31–34</sup> A recent study from Australia has challenged this finding: associating BV with non-penetrative genital contact and finding none in those denying all forms of genital contact.<sup>35</sup> BV was found in 17.5–29.3% of women having termination of pregnancy,<sup>36–39</sup> and the use of antibiotic prophylaxis with metronidazole decreases the risk of upper genital tract infection and infective morbidity after first trimester termination of pregnancy by about 50%.<sup>36,39</sup> BV is more prevalent in women with tubal infertility (31.5%) compared to those with

non-tubal infertility (19.7%).<sup>40</sup> About 29% of lesbian women attending a specialist clinic had BV as did 72.7% of their partners, again supporting a contribution from sexual transmission.<sup>41</sup>

## Pathogenesis

Lactobacillus species dominate normal vaginal flora, accounting for up to 96% of bacteria present. Most women with Lactobacillus dominant flora have H<sub>2</sub>O<sub>2</sub>-producing lactobacilli. *L. crispatus* and *L. jensenii* appear to be more protective against BV emerging than *L. gasseri*.<sup>42</sup> In contrast to normal women, one-third of the women with BV have no lactobacilli, and the remainder have lower concentrations of non-H<sub>2</sub>O<sub>2</sub>-producing lactobacilli. Lactobacilli are present at concentrations of 10<sup>5</sup> to 10<sup>8</sup> colony-forming units (CFU)/ml of vaginal secretions in normal women, and H<sub>2</sub>O<sub>2</sub> produced by certain strains of lactobacilli is inhibitory for certain bacteria in the vagina, particularly catalase-negative bacteria that do not have the enzyme that detoxifies H<sub>2</sub>O<sub>2</sub>.<sup>43,44</sup> H<sub>2</sub>O<sub>2</sub> may inhibit the growth of bacteria either directly via the toxic activity of H<sub>2</sub>O<sub>2</sub> or by reacting with a halide ion in the presence of cervical peroxidase as part of H<sub>2</sub>O<sub>2</sub>-halide-peroxidase antibacterial system.<sup>45</sup> These inhibit not only bacteria, but also HIV and other viruses *in vitro*.<sup>46</sup> Additional factors secreted by lactobacilli include peptides such as defensins and bacteriocins.

## Microbiology Studies Using Culture or DNA Probes

Hillier and associates described the frequency and concentration of microorganisms by isolation from the vagina of pregnant women,<sup>43</sup> stratified by the Gram stain criteria.<sup>47</sup> Based on the mean log concentration, Lactobacillus was present at concentrations 10 times greater (at log 10<sup>7</sup> levels) than that of the next most abundant microorganism, *G. vaginalis* (at log 10<sup>6</sup> levels). The number of lactobacilli is significantly decreased in BV; the concentration is about 10-fold less. The concentration of *G. vaginalis* is found at mean log of 10<sup>7.7</sup>, *Mycoplasma hominis* 10<sup>5.2</sup>, anaerobic gram-negative rods 10<sup>6</sup>, and *Prevotella bivia disiens* 10<sup>5</sup>.

In BV, lactobacilli comprise 1% or less of the bacteria present in the vagina.<sup>43</sup> Giorgi and colleagues identified *L. crispatus* and *L. jensenii*, not *L. acidophilus* and *L. fermentum*, as the predominant vaginal Lactobacillus species that colonize asymptomatic women.<sup>48</sup> This was later confirmed by Antonio and colleagues.<sup>49</sup> Using a whole-chromosomal DNA probe, most of the subjects were found to be colonized by *L. crispatus* (32%), followed by *L. jensenii* (23%), a previously undescribed species designated L. 1086V (15%), *L. gasseri* (5%), *L. fermentum* (0.3%), *L. oris* (0.3%), *L. reuteri* (0.3%), and *L. vaginalis* (0.3%). H<sub>2</sub>O<sub>2</sub> was produced by 95% of *L. crispatus* and 94% of *L. jensenii* isolates.<sup>50</sup>

## Studies Using Newer Molecular Techniques

Molecular techniques have so far required considerable resources, so many studies have sampled small numbers of subjects. Several investigators have used 16S RNA amplification and fluorescence

*in situ* hybridization (FISH) to identify hitherto unidentified bacteria in vaginal samples from women with BV. The use of different 16S RNA primers in different laboratories produces variation<sup>51</sup> and the sequences do not completely match the target organism for all bacteria leading to underquantification of some. Despite this, the results from different labs show that some asymptomatic women have a flora consisting of solely or predominantly lactobacilli, others a mixed flora with many BV associated organisms and some less expected patterns such as solely Streptococci or predominantly Pseudomonas. These studies did not specify the stage of the menstrual cycle which could impact significantly on the flora identified.

Verstraelen and colleagues studied the flora of 100 pregnant and non-pregnant women with similar methodology.<sup>52</sup> Thirteen had BV or intermediate flora. They identified several novel bacteria from women with BV and stressed the association with *Atopobium vaginae*. Fredricks and colleagues studied eight women with normal flora and nine with BV.<sup>53</sup> They identified novel bacteria in women with BV: BVAB1-3 which are classified as Clostridiales. Other novel organisms included *Atopobium vaginae*, *Leptotrichia amnionii*, *Sneathia species*, *Megasphaera species*, and Eggerthella-like bacteria. They were also able to follow subjects longitudinally and demonstrate changes in the organisms present in women who developed BV or who were treated successfully. The other organism of interest is *Lactobacillus iners*. This is a low H<sub>2</sub>O<sub>2</sub> producing organism, found in 99% of women with BV and 92% of women with normal flora. It stains as a small gram-negative bacillus. In a subsequent study Fredricks and colleagues concluded that detection of appropriate organisms by PCR could be used for diagnosis of BV with sensitivities and specificities of 94–99%.<sup>54</sup>

The description of the biofilm that develops in BV by Swidsinski and colleagues<sup>55</sup> places *Gardnerella vaginalis* once again at the center of pathogenesis of BV. Using a broad range of fluorescent bacterial group-specific rRNA-targeted oligonucleotide probes they identified a biofilm, adherent to epithelial cells in vaginal biopsies from women with BV. In some women the biofilm covered the entire biopsy, in others it was more patchy. *Gardnerella* accounted for 90% of bacteria seen in the biofilm, with *Atopobium vaginae* the only other numerically important organism. Lactobacilli predominated in women with normal flora, but did not form a biofilm. They proceeded to look at biopsies from a small number of women following treatment with standard courses of oral metronidazole.<sup>56</sup> Three different subjects were biopsied each week following treatment allowing a cumulative follow-up of 5 weeks. The biofilm persisted even at one week after treatment, although the bacteria were metabolically less active shown by low amenability. The amenability appeared to increase with time, although only one subject relapsed to intermediate flora at the time of biopsy. The hypothesis that persistence of the biofilm after treatment is associated with relapse appears highly plausible.

The primary etiology of BV is uncertain. Some authors regard it as an imbalance of endogenous flora, whilst others hold that there is a sexually transmitted pathogen as a necessary cause.



## Risk Factors

These are summarized in Table 44.1. BV has many behavioral associations characteristic of an STI such as change of sex partner, condoms providing protection and an association with STIs.<sup>57–60</sup> However it can be regarded as “sexually enhanced,”<sup>61</sup> rather than exclusively sexually transmitted. The best evidence against sexual transmission is its occurrence in virgin women at a similar prevalence to non-virgin women in three cross sectional studies.<sup>31,34,62</sup> An Australian study however reported the absence of BV in women with no genital contact at all, suggesting that “true virgins” may not have BV.<sup>63</sup>

Gardner and Dukes, in an attempt to fulfill Koch’s postulates for *Gardnerella*, induced BV in very few women inoculated with a culture of organism, but in a high proportion of those receiving vaginal discharge from women with BV.<sup>64</sup> The high concordance of lesbian couples for BV status again suggests transmission of BV from one to the other.<sup>41,65</sup> Thus, in monogamous lesbian couples, BV was reported in 72.7% of women whose partners had BV, compared to 10% of those whose partner did not have BV.<sup>74</sup>

Vaginal pH may be critical in the development of BV. *In vitro* anaerobes do not grow in the presence of *Lactobacilli* at pH 4.0 but escape at pH 6.0.<sup>45</sup> Estrogen levels alter over the course of a menstrual cycle, being highest in the luteal phase when BV is less common.<sup>66</sup> The numbers of *Lactobacilli*, and proportion of women colonized by BV-associated organisms changes with mid-cycle. Semen has an alkaline pH, between 7 and 8, and it is estimated that vaginal *Lactobacilli* produce enough acid to reduce pH by 0.56–0.75 units/hour.<sup>67</sup> Therefore, frequent unprotected sex may trigger BV through raising the pH. Factors that disturb vaginal physiology such as vaginal douching<sup>68,69</sup> pessary use,<sup>70</sup> and malodorous gynecological cancer<sup>71</sup> appear to increase the risk of BV. Recent antibiotic intake,<sup>46,72</sup> oral contraceptive pills,<sup>68,73–75</sup> and condom use<sup>74</sup> have not been related to BV.

BV is associated with HIV in cross sectional studies<sup>76,77</sup> and in a prospective study of pregnant women in Malawi, in which women with BV were more likely to seroconvert during pregnancy (OR 3.7) and postnatally (OR 2.3).<sup>78</sup> However, BV is associated with genital

herpes,<sup>79</sup> itself a strong risk factor for HIV acquisition. Studies that do not control for herpes should therefore be regarded as preliminary.<sup>80</sup> Only one small study has examined the relationship between BV and non-gonococcal urethritis (NGU) in male partners.<sup>81</sup> There were 39 men with NGU. Female partners of 12 (31%) had BV, compared to only 1 (8%) of the female contacts of the 12 men without NGU. In most studies BV is more common in women diagnosed with STIs including herpes, Chlamydia, gonorrhea and pelvic inflammatory disease.<sup>82</sup> This is discussed further under complications. One further argument against BV being sexually transmitted is the failure of partner treatment to reduce the relapse rate of BV in treated women. Several studies show that the treatment, with metronidazole or clindamycin, of male partners of women with BV has little effect on the recurrence of BV.<sup>83–86</sup> If there is a sexually transmitted agent, it is therefore not readily eliminated in men by these antibiotics.

## Biochemical Changes

The bacteria associated with BV produce a number of virulence factors. These include lipopolysaccharidases, sialidases, and mucinases.<sup>87,88</sup> Some strains of *G. vaginalis* cause cleavage of secretory IgA.<sup>89</sup> Anaerobic bacteria produce aminopeptidases that degrade protein and decarboxylases that convert amino acids and other compounds to amines such as putrescine, cadaverine, and trimethylamine. These amines contribute to raising the vaginal pH and produce the characteristic smell of BV.<sup>90,91</sup> The ratio of succinate, produced by anaerobic metabolism, to lactate, produced by *Lactobacilli* is increased.<sup>92</sup> These microbial substances and virulence factors collectively play a role in overcoming cervical host defense barriers leading to the ascent of microbes into the upper reproductive tract. They collectively cleave mucus leading to the thin homogenous discharge that is characteristic of BV. Transport of BV microflora and their products contributes to deciduitis and fetal membrane infection during pregnancy.<sup>88</sup>

The enzymes produced by bacteria found in BV can cleave IgA<sup>89</sup> and other protective factors such as secretory leukocyte protease inhibitor (SLPI). SLPI is found in saliva and vaginal fluid and inhibits HIV entry into cells. Levels were significantly reduced in vaginal fluid from women with BV.<sup>93</sup> Although BV has not been studied as risk factor for female to male transmission of HIV, women with HIV shed more virus into the cervico-vaginal discharge when BV is present.<sup>94</sup>

## Clinical Manifestations

In clinical practice the typical symptoms of BV are an unpleasant fishy smell and thin discharge.<sup>95,96</sup> In some women one or other manifestation predominates. Gardner commented that “practically all patients with BV were conscious of a disagreeable odour.”<sup>92</sup> The smell is more obvious after unprotected intercourse or with menstruation when elevated pH makes the amines more volatile.<sup>97</sup> About half the women with BV do not report any symptoms.<sup>98,99</sup> There is usually no inflammation. Occasionally women develop soreness of the vulva from maceration due to continual wetness.

**Table 44.1:** Risk Factors for Bacterial Vaginosis

Factors positively associated with BV	Factors negatively associated with BV
Black ethnicity	Oral contraceptive use
Intrauterine contraceptive device*	Condom use
Smoking	
Vaginal douching	
New male or female sex partner	
Receptive cunnilingus or anal sex	
Sexually transmitted infections, e.g., Chlamydia, HSV-2	

\*A recent review of the relationship between BV and intrauterine contraceptive device concluded that there is no convincing evidence of an association.<sup>204</sup> Studies that reported one did not adjust for confounding factors adequately.

On examination the discharge is described as milky or homogeneous, low in viscosity, white or grayish, and free of grossly visible crumbs of epithelial cells that are seen in normal vaginal secretion (flocular). Sometimes it is frothy, although this is usually seen with trichomoniasis. The fishy smell may be readily detected during examination in some women.

Whilst the clinical presentation of BV is easily recognized it is surprising that in a study of 2888 women attending for routine healthcare in Birmingham, Alabama women with BV did not report vaginal symptoms any more than women without BV.<sup>100</sup> Women with gonorrhea, Chlamydia, or trichomonas were excluded. In the past 6 months 75% of women with and 82% of women without BV never noted any vaginal odor. The corresponding values were 63% and 65% for never noting vaginal “wetness”; 58% and 57% for vaginal discharge; 91% and 86% for irritation; 88% and 85% for itching; and 96% and 94% for dysuria, respectively. Cumulatively, 58% of women with BV noted odor, discharge, and/or wetness in the past 6 months compared with 57% of women without BV.

In a gynecology clinic, around 49% of women with BV complained of malodor, compared with 20% without BV.<sup>98</sup> The reasons for this are complex but include embarrassment, believing it is a reflection of their personal hygiene, or normal. On the other hand some women experience stigma and discrimination because they perceive that others are detecting the smell. Thus, although BV is usually a benign condition, its symptoms make it an important cause of mental distress.

## Diagnosis

The presenting symptoms alone are not reliable for the diagnosis of BV. It can co-exist with the other common causes of abnormal discharge: candidiasis, trichomoniasis, and cervicitis, leading to atypical symptoms and signs. Even when BV is the only abnormality present it can be atypical.

The Amsel criteria are used for clinical diagnosis in many settings.<sup>101</sup> At least three of the following four signs must be present:

- Vaginal pH > 4.5,
- Homogeneous discharge,
- Positive amine test,
- Clue cell constituting 20% or more of total vaginal epithelial cells.

Clue cells, first described by Gardner as giving “a clue to the diagnosis,”<sup>92</sup> are epithelial cells coated with a thick film of small bacteria such that the border of the cell is obscured. The amine test is positive if addition of alkali, traditionally 10% KOH releases a strong fishy smell. These simple clinical tests are inexpensive and available in most office settings, requiring narrow range pH paper, 10% KOH, and saline, a microscope slide and microscope. Their limitations have been discussed many times. They all require subjective interpretation, and cannot be verified subsequently without re-examining the patient. The presence of clue cells is the most specific sign, but the specificity was increased by using a cut-off of at least 20% epithelial cells being clue cells.<sup>98</sup> Typical

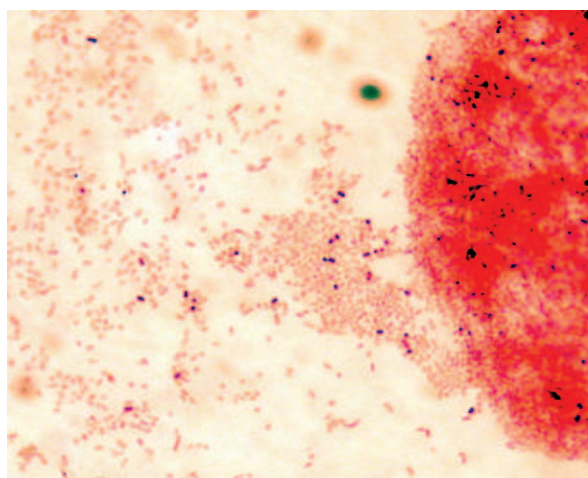
discharge may not be apparent even to the experienced observers: in one study this was the least reliable sign.<sup>102</sup> The amine test has low sensitivity,<sup>98</sup> and may be falsely positive if semen is present. The liquefaction of the semen may yield a homogeneous secretion, and raise the pH level as well.<sup>95</sup> If cervical mucus is inadvertently sampled it yields a pH as high as 7.0. Recent use of vaginal douches or medications may also cause diagnostic difficulty. Smears from women with trichomoniasis are usually deficient in Lactobacilli and have a high number of polymorphonuclear cells, but may not have typical clue cells to allow a definitive diagnosis of co-existent BV. Since the antibiotic treatment is the same the distinction is irrelevant for clinical practice.

One further limitation with the Amsel criteria is that they define a cut-off between normal and BV. It is now clear that there is a continuum between normal and BV in terms of the concentrations of bacteria present and the diversity of the vaginal flora. This makes it almost impossible for there to be 100% agreement between different diagnostic modalities. The systems for interpreting Gram-stained vaginal smears that were developed subsequently recognize intermediate grades of flora which increases precision in research studies. Nevertheless, the Amsel criteria are generally very good at identifying symptomatic patients in clinical practice.

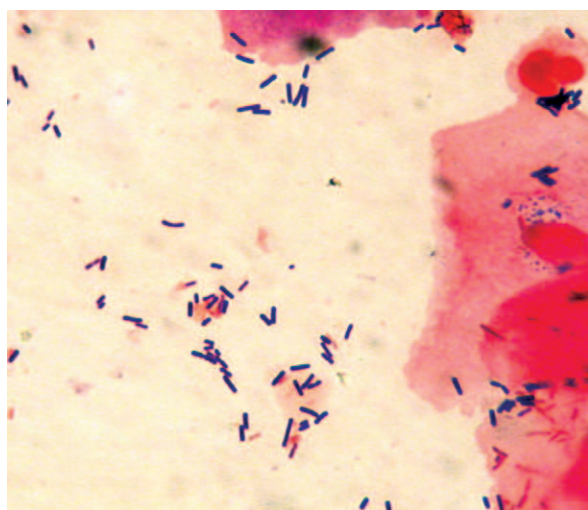
BV is readily recognizable on Gram stain of vaginal fluid (Fig. 44.1). Slides can be stored for months and verified independently, which allows quality control in multi-centre studies. Intermediate grades of flora can be recognized. The reagents used are inexpensive and readily available. Absent or reduced lactobacilli are replaced by high concentration of Gardnerella morphotypes sometimes accompanied by curved rods (*Mobiluncus* morphotypes). Nugent and colleagues provided a method to standardize the Gram stain interpretation of BV.<sup>47</sup> A score between 0 and 10 is derived from a weighted combination of the following: (i) large gram-positive rods (lactobacilli), (ii) small gram-negative or variable rods (*Prevotella* spp. or *G. vaginalis*), and (iii) curved gram-negative or variable rods (*Mobiluncus* spp.). Each group is quantitatively weighted on a scale of 0 to 4:

- 0 = no morphotype per oil field;
- 1+ = less than one morphotype per oil field;
- 2+ = one to four morphotypes per oil field;
- 3+ = five to 30 morphotypes per oil field;
- 4+ = more than 30 morphotypes per oil field.

Plentiful Lactobacillus morphotypes are considered normal: therefore the score is inversely related to the number of organisms: 4+ lactobacillus scores 0, 3+ scores 1 and so on. For Gardnerella morphotypes the score correlates to the number of organisms: 4+ Gardnerella gives a score of 4 and so on. Mobiluncus is similarly correlated but weighted lower, so 1+ and 2+ organisms scores 1 and 3+ and 4+ score 2. Therefore a Gram stain with “severe BV” scores 10: 4 for absence of Lactobacillus morphotypes; 4 for 4+ Gardnerella morphotypes; and 2 for 4+ Mobiluncus morphotypes. A “normal” Gram stain scores 0: 0 for 4+ Lactobacillus morphotypes, 0 for 0 Gardnerella morphotypes, and 0 for 0 Mobiluncus morphotypes.



\*c+



\*d+

**Fig. 44.1:** (a) Gram-stained vaginal smear from woman with BV, Nugent score 10. In the high power field there are no *Lactobacillus* morphotypes, greater than 30 *Gardnerella* morphotypes (curved rods), and between 5 and 30 *Mobiluncus* morphotypes (curved rods). The edge of an epithelial cell is shown on the right. It is covered with bacteria resembling a clue cell. (b) Gram-stained vaginal smear from a woman with normal flora, Nugent score 0. The flora is dominated by *Lactobacillus* morphotypes (Gram-positive rods, >30/high power field). The edges of the epithelial cells are seen clearly, with few bacteria. There is a polymorphonuclear cell at the top right corner.

A total score of 7 to 10 (the sum of rating score of those three groups) is considered to be indicative of BV, a score of 4 to 6 intermediate flora, and 0 to 4 normal flora. The sensitivity and specificity of Nugent's criteria, compared with Amsel's criteria were 83.3% and 92.1%, respectively<sup>103</sup> but Nugent scoring requires a skilled operator and can be time consuming.

In the UK a simpler method is recommended for use in Genitourinary Medicine clinics. The Hay–Ison criteria relies

more on pattern recognition, assessing the relative proportions of bacterial morphotypes.<sup>104,105</sup>

- Grade I (normal flora), *Lactobacillus* morphotype only or pre-dominant
- Grade II (intermediate flora), reduced *Lactobacillus* morphotype with mixed bacterial morphotypes;
- Grade III (BV), mixed bacterial morphotypes with few or absent *Lactobacillus* morphotypes.

Two additional grades are used also;

- Grade 0, epithelial cells with no bacteria seen
- Grade IV, epithelial cells covered with Gram positive cocci only

In an international workshop the inter-observer variability using the Nugent and Hay scoring systems was equally good for both.<sup>106</sup>

Detection of biochemical changes in vaginal fluid is an alternative way of making the diagnosis but not often used routinely. Gas-liquid chromatography had 78% sensitivity and 81% specificity in pregnant women.<sup>107</sup> Several criteria for abnormality were used: a succinate:lactate ratio greater than or equal to 0.4 or elevated peaks of acetate, propionate, isobutyrate, or isovalerate. The commercially available point-of-care test BVBlue measures sialidase, and performs well.<sup>108</sup> A recent evaluation reported sensitivity of 88% compared to both Nugent and Amsel criteria with specificity of 95% and 91%, respectively.<sup>109</sup>

Traditional qualitative culture is not reliable for diagnosis. Up to 60% of women without BV are colonized with *G. vaginalis*.<sup>17,107</sup> Therefore, isolation of *G. vaginalis* for diagnosis of BV without additional indicators is not helpful. High concentrations do correlate better with BV,<sup>110</sup> but quantitative aerobic and anaerobic vaginal cultures are costly and impractical for clinical use.<sup>111,112</sup> The Affirm VPIII uses DNA hybridization to detect high levels of *Gardnerella*. A recent evaluation reported a sensitivity of 87.7% and a specificity of 96.0% compared to Nugent scoring.<sup>113</sup>

Another test is the FemExam (Litmus Concepts Inc., Santa Clara, CA). FemExam card 1 has indicators for pH greater than or equal to 4.7 and one for amines greater than 0.5 mmol, card 2 measures proline iminopeptidase activity. A recent evaluation against Nugent criteria reported that FemExam card 1 had a sensitivity of 71.4% and specificity of 72.8%, FemExam card 2 a sensitivity of 70% and specificity of 81.0%.<sup>114</sup> and FemExam cards 1 and 2 combined had a sensitivity of 91.0% and specificity of 61.5%. Such tests may have some utility where there is no access to a microscope but incur greater reagent costs.

It is likely that identifying some of the newly identified bacteria found in BV using molecular techniques will provide highly specific and sensitive diagnosis of BV. When such tests become available they may replace Gram stain reading in research studies and eventually for clinical diagnosis if they become affordable. Detection of either *Megasphaera* or one of the *Clostridiales* bacteria (BVAB1-3) gave a sensitivity of 99% and specificity of 89% compared to Amsel criteria and a sensitivity of 95.9% and a specificity of 93.7% compared to Nugent criteria.<sup>54</sup> Fredricks and colleagues concluded



that “PCR detection of one or more fastidious bacterial species is a more reliable indicator of BV than detection of bacteria, such as *Gardnerella vaginalis*, previously linked to BV, highlighting the potential of PCR for the diagnosis of BV.”

## Complications

The symptoms of BV can be distressing for those with frequent recurrences. It can adversely affect sexual and family relationships and working lives, and lead to depression. BV is associated with an increased risk of many adverse outcomes summarized in Table 44.2.

In cross-sectional<sup>76,77,115</sup> and prospective studies<sup>78</sup> BV was a risk factor for acquisition of HIV (discussed in risk factors). In a prospective study of 657 Kenyan commercial sex workers absence of lactobacilli was predictive of acquiring HIV-1 infection (HR, 2.0; 95% CI 1.2–3.5) and gonorrhea (HR, 1.7; 95% CI, 1.1–2.6).<sup>50</sup> Presence of abnormal vaginal flora on Gram's stain was associated with increased risk of both HIV-1 acquisition (HR, 1.9; 95% CI, 1.1–3.1) and Trichomonas infection (HR, 1.8; 95% CI, 1.3–2.4). An interesting study of 255 women presenting as contacts of male partners with Chlamydia or gonorrhea found that those with BV were more likely to harbor *Neisseria gonorrhoeae* (OR 4.1; 95% CI, 1.7–9.7) and/or *Chlamydia trachomatis* (OR 3.4; 95% CI, 1.5–7.8).<sup>116</sup> This does not mean that BV necessarily increases susceptibility to STIs as it is possible that the STIs alter the vaginal environment, maybe through increased production of purulent cervical discharge of high pH, triggering BV. However, a prospective study that used serology to identify women with HSV-2 infection found that those with BV at baseline had a twofold greater risk of seroconversion over the course of a year.<sup>79</sup> In an intriguing study 107 women attending an STD clinic with asymptomatic BV were randomized to receive a 5-day course of metronidazole gel followed by twice weekly use for six months, or no treatment.<sup>117</sup> Either due to a lack of efficacy of the regimen or poor adherence BV recurred in more than 50% women in the metronidazole group, and regressed in about 30%

of those allocated to no treatment. Nevertheless, there was a significant reduction in the rate of Chlamydia infection over 12 months (3/53, 8.6% vs. 13/54, 27.1%), although not for other STIs. The accompanying editorial recognized the difficulties of performing this type of study, and its limitations and concluded that there is not sufficient evidence to recommend such an approach routinely.<sup>118</sup> Urinary tract infection in women is linked to persistence of *E. coli* in the vagina. Since lactobacilli inhibit *E. coli*, it is not surprising that BV was associated with a nearly threefold increased rate of UTI in a cross-sectional study.<sup>119</sup>

Many bacteria recovered from the tubes and pelvic abscesses of women with PID are those associated with BV.<sup>120,121</sup> In cross sectional studies BV is more prevalent in women with PID than those without.<sup>93</sup> Plasma cell endometritis, which is a histological correlate of PID, was associated with BV, albeit only just reaching statistical significance (15, 95% CI 2–686).<sup>122</sup> The GIFT study prospectively evaluated 1179 women over up to four years.<sup>123</sup> BV was associated with endometritis in a subset of 278 women (OR, 2.4; 95% CI, 1.3–4.3).<sup>124</sup> BV alone was not a risk factor for PID, but amplified the risk of PID three-fold if there was concurrent Chlamydia or gonorrhea (OR 3.1; 95% CI, 1.64–5.87).

BV is linked to infections after pelvic surgery. Thus women with BV had higher rates (RR 3.2; 95% CI, 1.5–6.7) of cuff cellulitis after abdominal hysterectomy.<sup>125</sup> In a Swedish study cuff cellulitis or wound infection occurred in 35% (7/20) of those with BV and 8% (4/50) (OR 6.2; 95% CI, 1.3–30.7) of those without BV.<sup>126</sup> BV is a risk factor for endometritis after surgical termination of pregnancy. Clue cells identified pre-operatively were associated with an 5.6-fold (95% CI, 1.8–17.2) increased risk of infection.<sup>127</sup> Several RCTs of treatment before termination have shown benefit: Larsson and colleagues reported a 3-fold reduction with 10 days oral metronidazole in a study of 174 women,<sup>128</sup> and a 4-fold reduction from use of clindamycin cream.<sup>129</sup> In the UK, Crowley and colleagues reported a 50% reduction with a single 2 g suppository of metronidazole, but this just failed to reach statistical significance.<sup>39</sup> A study from the USA did not demonstrate a significant benefit, but there was trend for benefit from oral metronidazole in the 154 women with BV (RR 1.6; 95% CI, 0.9–3.0).<sup>130</sup> Most women undergoing Caesarean section currently receive antibiotics including metronidazole. In a setting before this became the practice, BV was associated with a 6 fold increased risk of postpartum endometritis.<sup>131</sup> In a randomized study of women with or without BV, a single intravaginal dose of metronidazole reduced the risk of post-Caesarean endometritis by 60% (RR 0.42; 95% CI, 0.19–0.92).<sup>132</sup>

## PREGNANCY COMPLICATIONS

Complications following termination of pregnancy and Caesarean section have been discussed in the previous section. BV has been associated with complications throughout pregnancy. Endometritis, which is associated with BV, is likely to be unfavorable to implantation. Thus, in women undergoing IVF isolating H<sub>2</sub>O<sub>2</sub> producing lactobacilli or no bacteria from the tip

**Table 44.2:** Complications Associated with Bacterial Vaginosis

All women:
Acquisition of sexually transmitted infections, including HIV, Gonorrhea, Chlamydia, HSV
Urinary tract infection
Upper genital tract infection: spontaneous PID and post-abortion endometritis
Post hysterectomy cuff cellulitis and wound infection
Pregnancy:
Reduced chance of successful IVF
Second trimester miscarriage
Spontaneous pre-term birth, pre-term pre-mature rupture of membranes, low birth weight
Post Cesarean section endometritis

of the catheter used for implantation of an embryo is associated with a higher rate of successful pregnancy, and isolating bacteria associated with BV with poorer outcome.<sup>133</sup> In a UK study BV was associated with a greater rate of early pregnancy loss in women undergoing IVF (OR 2.67; 95% CI, 1.26–5.63).<sup>134</sup>

During pregnancy chorioamnionitis, which is strongly associated with pre-term birth, can develop from bacteria already present in the endometrium or those continuing to ascend from the vagina.<sup>135</sup> Further spread leads to deciduitis, amniotic fluid infection, fetal infection and ultimately fetal death from sepsis. The release of inflammatory mediators including IL-1, IL-6, and TNF- $\alpha$  stimulate production of prostaglandins, the final pathway for initiating labor. The cytokines, endotoxins, and exotoxins also initiate neutrophil chemotaxis, infiltration, and activation, leading to release of metalloproteases which denature the membranes, leading to rupture and they also soften the cervix.<sup>136</sup>

Many studies have investigated the relationship between BV and adverse pregnancy outcomes. Initial case control studies demonstrated an association before prospective cohort studies confirmed it. BV is associated strongly with second trimester miscarriage, with odds ratio up to 5.<sup>105,111</sup> BV is associated with intra-amniotic fluid infection,<sup>137,138</sup> chorioamnionitis leading to pre-term delivery,<sup>139</sup> pre-mature rupture of membranes (OR 7.3).<sup>140</sup> A meta-analysis in 2003 concluded that BV doubles the risk of pre-term birth (OR 2.19; 95% CI, 1.54–3.12).<sup>141</sup> The largest single study from the USA involving 12,937 women reported a smaller effect (OR 1.2; 95% CI, 1.1–1.4).<sup>142</sup> Two recent studies using modified criteria for diagnosis reported that lack of lactobacilli, and/or markers of inflammation were stronger predictors of adverse outcome than BV. Donders and colleagues include aerobic vaginitis, in which there are reduced lactobacilli with parabasal cells, cocci and coliforms, and neutrophils.<sup>143</sup> They found that such disturbed flora, and absence of lactobacilli were more predictive of pre-term birth than standard BV.<sup>144</sup> Verstraelen and colleagues identified a variant of normal flora<sup>145</sup> accompanied by atypical gram-positive bacteria and neutrophils which was more strongly associated with pre-term birth than BV,<sup>146</sup> with an odds ratio of 5.2 (95% CI, 1.8–14.5).

The microorganisms found in BV are also commonly found in the amniotic fluid of women with amniotic fluid infection.<sup>147</sup> Bacteria associated with BV make up about one half of the isolates from amniotic fluid of women in pre-term labor with intact membranes.<sup>148</sup> Using a combination of culture and PCR DiGiulio and colleagues identified bacteria in 15% of 166 women presenting in pre-term labor with intact membranes.<sup>149</sup> All these women delivered pre-term and had greater rates of chorioamnionitis (OR 20; 95% CI, 2.4–172). In a subsequent paper they showed that the presence of bacteria was associated with higher levels of polymorphs and IL-6.<sup>150</sup> The range of bacteria identified are shown in Fig. 44.2. They are predominantly BV-associated or Ureaplasma.

In summary there is good evidence that BV/abnormal vaginal flora is predictive of spontaneous pre-term birth and that the majority of bacteria found in chorioamnionitis and amniotic

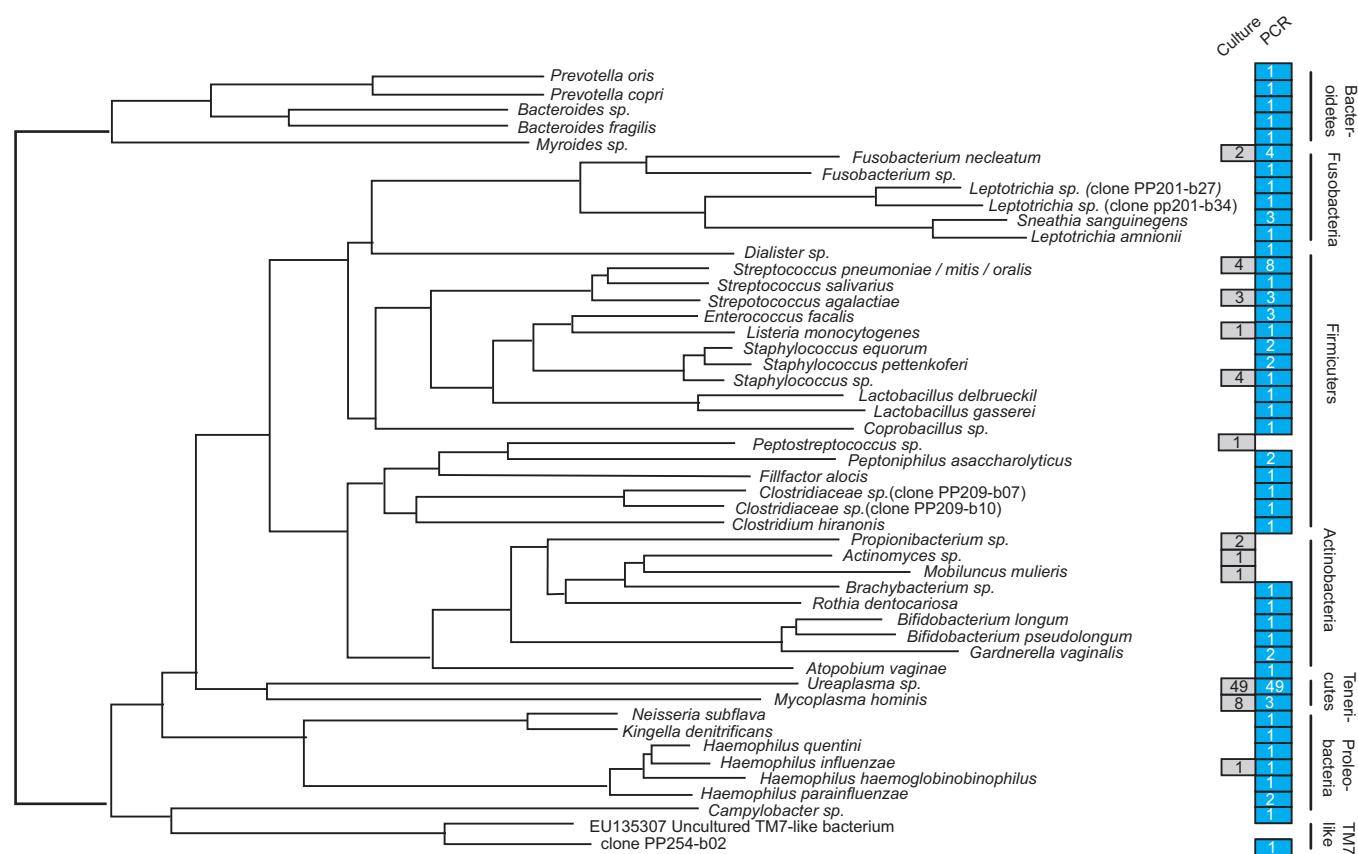
fluid infection are BV-associated or Ureaplasma. Furthermore, the presence of bacteria is associated with an inflammatory response and pre-term birth. Identifying and treating BV early in pregnancy might therefore be expected to reduce adverse pregnancy outcome.

Several studies have investigated the use of oral metronidazole,<sup>151–153</sup> oral clindamycin,<sup>154,155</sup> and topical clindamycin<sup>88,156–159</sup> in the second or third trimester of pregnancy to treat BV as a way of preventing pre-term birth (PTB). One study used a combination of erythromycin and metronidazole.<sup>160</sup> Some studies showed a statistically significant reduction in late miscarriage,<sup>154</sup> and pre-term birth,<sup>151,154,155,159,160</sup> some no difference,<sup>88,152,153</sup> and some a trend for worse outcome with topical clindamycin treatment.<sup>156–158</sup> Systematic reviews have reached varying conclusions: including Cochrane which concluded “... little evidence that screening and treating all pregnant women with asymptomatic BV will prevent PTB and its consequences. However, there is some suggestion that treatment before 20 weeks’ gestation may reduce the risk of PTB.”<sup>161</sup> U.S. Preventive Services Task Force found that “No benefit was found in treating women with low- or average-risk pregnancies for asymptomatic bacterial vaginosis.”<sup>162</sup> A Canadian review concluded that “Macrolides and clindamycin, given during the second trimester of pregnancy, are associated with a lower rate of pre-term delivery, whereas second-trimester metronidazole used alone is linked with a greater risk of pre-term delivery in a high-risk population.”<sup>163</sup> Neither US CDC guidelines, nor UK recommend routine screening and treatment for BV, but allow the clinician to decide in high risk pregnancies.

One further study should be mentioned. Kiss and colleagues in Vienna screened 4429 women for BV, candida and Trichomonas in the second trimester of pregnancy.<sup>164</sup> Those randomized to intervention were treated with topical clotrimazole, clindamycin and metronidazole respectively. There was a reduction in pre-term birth for the intervention group: 3.0% vs. 5.3% (95% CI 1.2–3.6). Surprisingly most of the difference was in women treated for candida rather than BV, and very few had Trichomonas. This study needs replicating, but supports the concept of treating vaginal infections to prevent pre-term birth.

## Treatment

Treatment is indicated for symptomatic BV. If “asymptomatic” BV is found many clinicians discuss the specific symptoms in detail as they may have been concealed initially due to embarrassment. Genuinely asymptomatic BV does not need treatment. Even though BV is associated with many adverse sequelae there is no evidence that treating it makes a substantial difference to whether it will be there subsequently, except possibly in pregnant women in whom BV appears to occur at a low rate.<sup>165</sup> In the Rakai study of mass treatment for STIs to prevent HIV infection there was no reduction in the prevalence of BV following mass treatment of men and women with metronidazole and other antibiotics except in women who were pregnant.<sup>24,166</sup> The GYN Infections follow-through Study (GIFT) recruited predominantly young



**Fig. 44.2:** Microbial diversity of bacteria found in amniotic fluid of women in pre-term labor. Microbial diversity: Phylogeny of the 17 bacterial taxa identified in this study, based on a maximum likelihood algorithm. Colored boxes indicate the number of subjects who were positive for a given taxon by culture (gray) or PCR (blue) (some samples were polymicrobial). For most individual taxa, the larger of the two numbers in the corresponding gray or blue box represents the total number of positive subjects; for taxa where neither method detected all positive subjects, the total number is shown in the white box. A 99% sequence similarity cutoff threshold was used for phylotype assignment, which was based on 621 unambiguous nucleotide positions. *Bergeyella* sp. (bracketed and in gray type) is included as a reference species only and was not detected in the study population. A single fungal species, *Candida albicans*, was detected by culture in 1 subject and by PCR in 2 (data not shown). Reproduced from reference 149.

black women considered to be at high risk for STI acquisition.<sup>167</sup> Ness and colleagues showed that the likelihood of changing Nugent score between visits (every 6 or 12 months) was normally distributed; that is, BV resolved in as many women as in whom it developed.

After Gardner and Dukes<sup>2</sup> identified what we now call *G. vaginalis*, therapy was directed towards the organism with oral tetracycline, a triple sulfa vaginal cream and subsequently ampicillin. Metronidazole and clindamycin were employed after the importance of anaerobic organisms was recognized in the late 1970s.<sup>168</sup> The clinical definition of BV makes evaluation of treatment difficult: it includes women without symptoms, who may not need treatment, and there has not been a standard definition of cure, for example, less than 3 Amsel criteria or none? Variations in the reported therapeutic efficacy often can be attributed to a number of methodological differences, such as different study populations, diagnostic criteria, length of follow-up, and definition

of cure. Duration of follow-up is probably the most important variable in determining the effectiveness. By current standards few comparative studies, other than those employing placebo have been adequately powered to show non-inferiority.

Most therapies recommended for BV in non-pregnant women are successful in the short term, but relapse over 1–3 months occurs in greater than 50% treated women. Metronidazole and clindamycin are the drugs studied most frequently and therefore recommended in guidelines. The current CDC guidelines favor metronidazole 400 mg twice daily for 7 days as the most reliable treatment, based on a detailed review of all published studies.<sup>169</sup> The estimated efficacy was 80–90%. Alternative treatments may be preferred by women with recurrent BV, or those for whom metronidazole is contra-indicated. These are oral metronidazole or tinidazole as a single 2 gram dose, topical metronidazole 0.75% gel applied daily for 5 days, or 2% clindamycin cream applied daily for 5 days.



Metronidazole was first introduced for the treatment of trichomoniasis. Its therapeutic use has subsequently been expanded to include protozoal and anaerobic infections, including BV. Metronidazole given orally is absorbed almost completely. Metronidazole has limited plasma protein binding and favorable tissue distribution. The drug is extensively metabolized by the liver to form 5-oxidative metabolites. Majority of the drug and its metabolites are excreted in the urine and feces. The half-life is 6 to 10 hours. Metronidazole is generally well-tolerated at less than 2 g per day, for short periods. The commonest toxicity is gastrointestinal, a metallic taste, anorexia and nausea which tends to increase over successive days. It has a disulfiram-like effect with alcohol leading to hangovers. Interactions with warfarin and phenytoin have been reported. Mutagenesis and carcinogenesis are only described in mice. Several meta-analyses have concluded that there is no evidence of teratogenicity in humans and it can be used in the first trimester of pregnancy.<sup>170–172</sup> Fortunately bacterial resistance, both clinical and microbiological, has been described only rarely.<sup>173</sup> Serum metronidazole concentrations after intravaginal administration of 0.75% gel were only 2% of the concentrations achieved with the standard 500 mg oral dose.<sup>174</sup> Not surprisingly systemic side effects are therefore uncommon.<sup>175,176</sup>

Clindamycin is also an effective treatment for BV, but is more expensive and is associated with diarrhea and, infrequently, pseudomembranous colitis.<sup>177</sup> It is also more active against lactobacilli, although this has not translated into reduced efficacy compared to metronidazole.<sup>178,179</sup> The oral dose of 300 mg twice daily has not been studied extensively outside of pregnancy, but appears to have efficacy similar to metronidazole.<sup>180</sup> The topical preparation of clindamycin contains mineral oils, which may weaken latex condom and diaphragms. There is less than 5% systemic bio-availability.<sup>181</sup> In non-pregnant women, topical clindamycin 2% vaginal cream or metronidazole vaginal gel have rates of cure similar to those for oral metronidazole.<sup>182–184</sup> However resistance in some bacteria such as *Prevotella* appears to be selected rapidly, leading to caution in long-term use of clindamycin.<sup>185</sup>

One complication common to all treatments is vaginal candidiasis. It has been reported in varying proportions: 8.5% after oral metronidazole,<sup>183</sup> 21% with metronidazole vaginal gel,<sup>186</sup> and 4.7% with clindamycin vaginal cream.<sup>183</sup>

Other agents, some with good anti-anaerobic activity, have been studied with cure rates reported as follows:

- Tinidazole, 2 g orally single dose—51%,
- Tinidazole, 2 g orally on 2 consecutive days—74%<sup>187</sup>; (Tinidazole was superior to placebo using stringent criteria for cure, using 1 gram daily for 5 days 36.8% were cured compared to 5.1% [ $p < 0.001$ ])<sup>188</sup>
- Secnidazole, 2 g orally single dose—59–96%<sup>189</sup>;
- Amoxicillin + clavulanic acid, 500 mg three times daily for 7 days—70%<sup>190</sup>; amoxicillin, 500 mg three times daily for 14 days—no significant difference compared with placebo<sup>191</sup>;

- Triple sulpha vaginal cream—41.8%<sup>192</sup>;
- Erythromycin, 500 mg orally twice daily for 7 days – 19%.<sup>193</sup>

## ALTERNATIVE TREATMENTS

Probiotics and prebiotics have been studied as a treatment for gastrointestinal conditions. Vaginal lactobacilli differ from those considered optimal for the gut, but several vaginal strains are now available. Another approach is to use lactic acid gel to acidify the vagina. Both approaches have been evaluated in small studies of variable quality so there is insufficient evidence to support their routine use in current guidelines.<sup>194–196</sup> They may however be useful adjunctive treatments.

## TREATMENT OF MALE PARTNER(S)

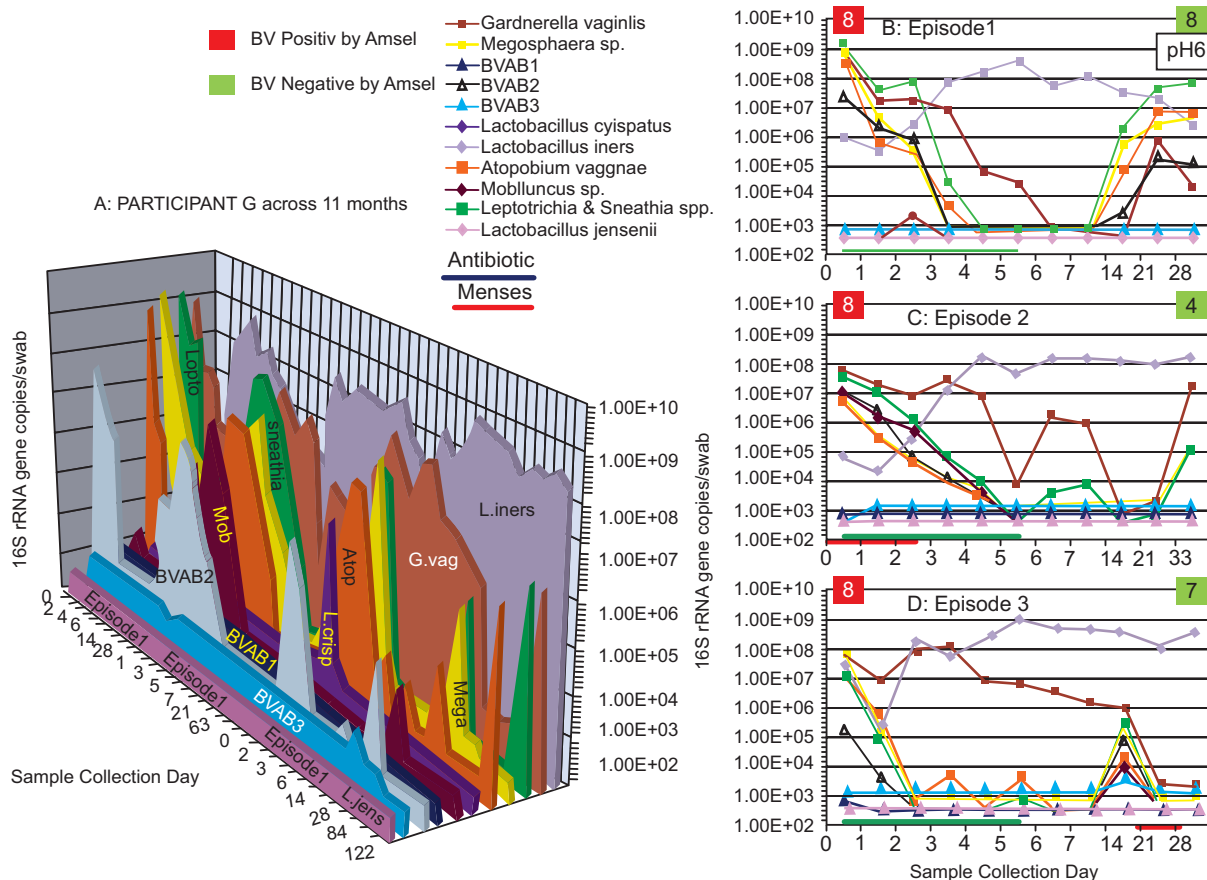
One of the arguments against BV being an STI is that treatment of male partners with antibiotics used for BV has not reduced the rate of recurrence in female partners.<sup>197</sup> Several randomized trials in which metronidazole therapy was given to male sexual partners of women with BV, failed to demonstrate any effect on the recurrence of BV.<sup>83–85</sup> One study used clindamycin for male partners and again found no difference in recurrence rates.<sup>86</sup> There is therefore no indication for treatment of male partners of women with BV. However, given the high rate of NGU reported in male partners of women with BV attending an STD clinic<sup>81</sup> it is reasonable to screen male partners of women with recurrent BV for STIs.

## Recurrent BV

The propensity of BV to recur remains frustrating for those affected by it, and in severely affected women, it can lead to depression and adversely affect relationships.<sup>195</sup> It is important at a public health level because we have not identified how to reduce many of the associated complications. Are the factors that trigger a first episode the same as those that trigger recurrence? The flora can be in a very dynamic state with rapid changes over the course of a menstrual cycle. This can be shown by collecting vaginal smears for Gram staining,<sup>198</sup> or more recently by quantitative 16S RNA detection,<sup>199</sup> shown in Fig. 44.3.

An Australian study followed a cohort of 121 women treated for BV with metronidazole for 7 days.<sup>200</sup> Over the course of a year 58% had a recurrence of BV, and 69% had a recurrence of abnormal vaginal flora (Nugent score 4–10) by 12 months. Recurrence was associated with a past history of BV; a regular sex partner throughout the study; and female sex partners.

How can we prevent relapse? Sobel and colleagues recruited 157 women with BV at presentation and a history of at least two episodes in the previous 12 months.<sup>201</sup> They randomized 112 women who had no symptoms of BV and fewer than three Amsel criteria positive after an initial 10-day course of metronidazole gel. They received metronidazole gel or placebo



**Fig. 44.3:** Temporal fluctuations in bacterial concentrations in a woman with recurrent BV. Bacterial fluctuations in a participant with recurrent BV: Figure A depicts dynamic patterns of BV bacteria in Participant G across a period spanning 11 months. She was diagnosed with BV by Amsel's and Nugent's criteria at entry (Episode 1, B), and was responsive initially to treatment. However, she had two more episodes subsequently (C and D) and each time she responded to metronidazole treatment but had a return of BV-associated bacteria and went on to develop BV. Reproduced from Srinivasan et al.<sup>199</sup>

twice weekly for 16 weeks with a further 12 weeks of follow-up off therapy. During suppressive therapy, there were recurrences in 13 women (25.5%) receiving metronidazole and 26 (59.1%) receiving placebo (RR 0.43; 95% CI, 0.25–0.73). By the end of week 28, however, recurrences occurred in an additional 13 women randomized to metronidazole gel and seven to placebo, which suggests little if any long-term benefit from suppression of this duration. Secondary vaginal candidiasis occurred significantly more often in metronidazole-treated women. An earlier single blind study showed that nystatin and metronidazole ovules produced a lower relapse rate than metronidazole gel alone.<sup>202</sup> It is the practice of the author to prescribe weekly antifungal treatment with metronidazole gel suppression for women with recurrent BV and a history of vaginal candidiasis.

Might more prolonged courses of treatment, or combinations of antibiotics be more effective? Schwabke tested the hypotheses that adding azithromycin to a metronidazole regimen would improve cure because of greater activity against some BV organisms such as *Mobiluncus curtisii* and *Mycoplasmas*, or

that prolonging the duration of metronidazole therapy from 7 to 14 days would be more effective.<sup>203</sup> It was adequately powered with 568 women randomized across the 4 arms. Seven days after treatment finished there was a significant benefit for the 14-day course of MTZ compared to 7 days with 44.8% cured compared to 63.4%. This benefit was lost at day 21 after treatment completion, and there was no benefit from adding azithromycin to the regimen. Certainly neither approach seems to be the answer. It may be that combinations of treating male partners, probiotics and lactic acid gel are required. Even with metronidazole gel suppression twice a day some breakthrough occurs. There is also the same dilemma as in managing recurrent herpes and candida: the trials of suppressive therapy give data for 6 months, but patients need long-term management, and may require very prolonged suppression. If recurrence does not occur every month it is often preferable to give a woman several treatment courses to initiate treatment when symptoms recur so that she does not have to take time off to arrange an urgent appointment, and can feel in control when BV recurs.

## Summary

Bacterial vaginosis (BV) is highly prevalent among women of childbearing age; affecting between 5% and 50% of women in various populations. The symptoms can cause considerable distress, particularly in those most frequently and severely affected.

Debate continues as to whether it is a sexually transmitted condition or merely associated with intercourse and other infections. The recent description of a biofilm in which *Gardnerella vaginalis* and *Atopobium vaginae* predominate has again placed *Gardnerella* at the center of pathogenesis, and it may be that particular pathogenic strains are sexually transmitted.

BV is associated with infections following termination of pregnancy and other gynecological procedures. It is associated with STIs such as chlamydia and gonorrhoea, and is a risk factor for acquisition of HIV in women. In pregnancy, it is a risk factor for late miscarriage, idiopathic preterm birth, and post-caesarean section endometritis.

Oral metronidazole remains the mainstay of treatment; metronidazole and clindamycin vaginal treatments also available. Prevention of recurrent BV remains problematic, with limited benefit from alternative treatments with lactic acid gel or probiotics. Studies of antibiotics in pregnancy have yielded conflicting results, and routine screening and treatment with antibiotics is not recommended.

It is hoped that improved understanding of the pathogenesis of BV arising from studying biofilms and typing *Gardnerella* with molecular methods will lead to improved treatments and outcomes.

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# 45

## Pelvic Inflammatory Disease

Jonathan D.C. Ross

### Introduction

Pelvic inflammatory disease (PID) is inflammation of the endometrium, uterus, fallopian tubes, and adnexal structures, which usually occurs secondary to sexually transmitted infections of the lower genital tract. This differs slightly from “pelvic infection” which includes not only PID but also puerperal sepsis, post-abortion infections, and local pelvic infection secondary to surgery. PID is a common condition in young women and extremely costly,<sup>1</sup> both in financial terms and also due to the considerable physical and psychological morbidity that can follow.

### History

The two great Scottish venereologists of the 18<sup>th</sup> century, John Hunter (1728–1793) and Benjamin Bell (1749–1805), had conflicting opinions about the link between gonorrhea and PID—Hunter stating that “it has been asserted that the ovaria are sometimes affected ... I should very much doubt the possibility” but Bell correctly concluding that “In some cases the inflammation [from gonorrhea] spreads to ... the uterus and ovaria.”<sup>2</sup> Bell’s opinions were not widely accepted, however, and 100 years later, it was still generally believed that pelvic inflammation occurred secondary to obstruction of the lochia, uterine malposition, trauma, and/or excessive intercourse.<sup>2</sup>

Emil Noeggerath (1827–1894), German born but holding a chair in obstetrics and gynecology in New York, presented data from a large clinical cohort of women, suggesting that latent gonorrhea and associated PID were extremely common affecting up to two-thirds of the urban US population.<sup>3</sup> This proposal was met with anger and disbelief by his colleagues in the US and abroad, who felt that its implications on the moral standards of the general population were scandalous and unacceptable. The identification of the gonococcus in 1879 by Neisser vindicated Noeggerath but he died a broken man in 1894. The association of PID with gonorrhea and TB was thus recognized by the mid 19<sup>th</sup> century but it was another 100 years until the polymicrobial

nature of the infection became clear and the central role of *Chlamydia trachomatis* identified.

### Biology

Many organisms can be isolated from the upper genital tract of women with PID, often concurrently, but it remains unclear which are primary pathogens (Table 45.1). It is also difficult to make direct comparisons among bacterial flora isolated in different clinical studies because of differences in how samples were collected and analyzed. The best epidemiological and clinical evidence supports the role of sexually acquired *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, ascending from the endocervix to the endometrium and fallopian tubes. However, in 20–70% of PID, no organism will be isolated from the upper genital tract.<sup>4</sup> This may reflect clearance of an initial chlamydial or gonococcal infection secondary to the infected tissues becoming increasingly anaerobic, and/or involvement of as yet unidentified agents.

**Table 45.1:** Organisms Associated with Pelvic Inflammatory Disease

Aerobic	Anaerobic
<i>Neisseria gonorrhoeae</i>	<i>Bacteroides</i> sp.
<i>Chlamydia trachomatis</i>	<i>Peptostreptococcus</i> sp.
<i>Mycoplasma genitalium</i>	<i>Clostridium bifermentans</i>
<i>Gardnerella vaginalis</i>	<i>Fusobacterium</i> sp.
<i>Strep. pyogenes</i>	
Coagulase negative staphylococci	
<i>Escherichia coli</i>	
<i>Haemophilus influenzae</i>	
<i>Strep. pneumoniae</i>	
<i>Mycobacterium tuberculosis</i>	
<i>Ureaplasma urealyticum</i>	

## NEISSERIA GONORRHOEAE

*N. gonorrhoeae* can be isolated from the fallopian tubes in women with PID<sup>5,6</sup> and between 8% to 19% of those with cervical gonorrhea have signs of upper genital tract infection.<sup>7,8</sup> The absence of *N. gonorrhoeae* from the lower genital tract cannot exclude gonococcal PID, since it may only be isolated from the upper genital tract in some women.<sup>6</sup>

Certain subtypes of gonococci are particularly associated with PID including the AHU-auxotype and strains which are more resistant to antibiotics.<sup>9</sup> A number of virulence factors have also been identified, including the expression of pili on the surface membrane of the bacteria, which are involved in attachment to the host epithelial cells.<sup>10</sup>

## CHLAMYDIA TRACHOMATIS

*C. trachomatis* is an unusual bacterium because it requires the host cell structures to replicate and is therefore an obligate intracellular bacterium. This leads to potential difficulties in confirming the diagnosis because culture is only possible following inoculation of cell lines and chlamydia enzyme-linked immunoassays are insensitive. Nucleic acid amplification tests (NAATs) are, however, widely available and provide a rapid and sensitive alternative.

The role of *C. trachomatis* in the pathogenesis of PID is supported by the detection of the organism in the upper genital tract of women with clinical symptoms and signs of PID,<sup>11,12</sup> the high prevalence of anti-chlamydial antibodies in women with tubal obstruction,<sup>13</sup> and animal data demonstrating salpingitis after inoculation with *C. trachomatis*.<sup>14</sup> The concept of canalicular spread of infection from lower to upper genital tract, as opposed to hematogenous, lymphatic, or trans-peritoneal spread, is supported by studies in monkeys showing protection against salpingitis in those animals with ligated fallopian tubes.<sup>15</sup> The risk of developing PID in young women with lower genital tract chlamydia infection is approximately 10%.<sup>16</sup>

## MYCOBACTERIUM TUBERCULOSIS

A significant cause of PID in Western countries in the past, tuberculous PID is now largely confined to developing countries or immigrants from these countries.<sup>3</sup> Most cases occur secondary to an extra-genital infection but rare instances of sexual transmission can also occur.<sup>15</sup> *M. tuberculosis* is not usually isolated from the lower genital tract<sup>17</sup> and samples should be taken by uterine curettage, or via laparoscopy, for culture or PCR analysis to make a diagnosis. Chest x-ray, sputum culture, and early-morning urine samples for culture are also appropriate. Quadruple anti-tuberculous chemotherapy is effective, e.g., isoniazid, rifampicin, ethambutol, and pyrazinamide, but extensive pelvic involvement or fibrosis may require surgery.

## OTHER ORGANISMS

PID in the absence of *N. gonorrhoeae* or *C. trachomatis* is associated with more prolonged and recurrent disease.<sup>18</sup>

## Mycoplasma genitalium

*M. genitalium* is a common cause of sexually acquired urethritis in men and has been associated with cervicitis, endometritis, and salpingitis in women.<sup>19,20</sup> Direct inoculation of the organism in the lower genital tract of non-human primates causes salpingitis and oophoritis,<sup>21,22</sup> and women with tubal factor infertility are more likely to have immunological evidence of previous *M. genitalium* infection.<sup>23</sup> There is also a trend toward more adverse long-term sequel in women with PID in whom *M. genitalium* is detected.<sup>24</sup>

## Anaerobes

Laboratory evidence and animal studies suggest that anaerobes are important pathogens in PID and identify them as a specific target for treatment.<sup>25,26</sup> In the lower genital tract, the production of mucinases and sialidases<sup>27</sup> by anaerobes may facilitate the passage of bacteria through the cervical mucus plug leading to upper genital tract infection. Anaerobes can be found in the genital tract of 13% to 78% women with PID<sup>28</sup> and are associated with more severe disease, including abscess formation.<sup>29,30</sup> The presence of a wide variety of organisms have been reported including *Bacteroides fragilis*, peptostreptococci, and peptococci.<sup>31</sup>

## Association with Bacterial Vaginosis

An association with bacterial vaginosis (BV) is suggested by the higher rate of BV in women with PID,<sup>32–34</sup> and the similarity in organisms was found between the upper genital tract in PID and lower genital tract in bacterial vaginosis.<sup>35</sup> Also, treating BV appears to reduce the risk of PID in women presenting for termination of pregnancy.<sup>36</sup> Prospective studies have failed to find a direct causal link between BV and PID, but women with concurrent BV and gonorrhea or chlamydia, or those who have large numbers of anaerobic gram-negative bacteria in the vagina, do appear to be at increased risk of developing PID.<sup>37</sup>

## Actinomyces

Pelvic infection with *Actinomyces israeli* has been associated with intrauterine device (IUD) use but IUD removal and antibiotic therapy are only indicated when the woman has symptoms, which may include intermenstrual bleeding, pelvic pain, or vaginal discharge.<sup>38</sup>

## ADDITIONAL POTENTIAL PATHOGENS

*Mycoplasma hominis*, *Ureaplasma urealyticum*, and other bacteria have been isolated from the upper genital tract, but whether they represent true pathogens or are markers of sexual activity is not known.<sup>15,39</sup> It is also possible that viruses may account for some cases where bacterial culture is negative, e.g., coxsackie, echo, herpes simplex.<sup>15,40,41</sup> In a small number of cases, respiratory bacteria, such as *H. influenzae* and *Strep. pneumoniae*, are isolated suggesting a possible link with orogenital sexual contact.



## Epidemiology

PID is one of the commonest causes of morbidity in young women and affects approximately 1 million women each year in the US.<sup>1</sup> If cases presenting in the community are included, the prevalence is even higher—estimated at over 1 in 60 women of reproductive age in England and Wales.<sup>42</sup> Trends in PID rates parallel those of gonorrhea and chlamydia<sup>43</sup> (Fig. 45.1), but lag behind by several months as can be seen in the increasing rates of PID in the UK in 1970s and 1980s<sup>44,45</sup> and decreasing rates in the US in the 1990s.<sup>46</sup>

The peak incidence of PID is between the ages of 15 and 25 years.<sup>46</sup> Those communities which have a large young population are therefore at particular risk, including developing countries. This increased risk is related to both high-risk sexual behavior in this age group, and probably also greater susceptibility to PID secondary to cervical ectopy, more penetrable cervical mucous, and lower levels of anti-chlamydial antibodies. Since not all women develop PID following lower genital tract infection, it is likely that susceptibility is also genetically determined and an association with HLA-A31 has been described.<sup>47</sup>

Not surprisingly, some of the risk factors for PID are similar to those for chlamydia and gonorrhea:

- multiple sexual partners
- a past history of sexually transmitted disease in the patients or their partner
- lack of condom use.<sup>48</sup>

Other risk factors seem to be linked to the spread of infection from the lower to the upper genital tract:

- douching is more commonly reported in women with PID,<sup>49,50</sup> particularly in certain ethnic sub-groups, e.g., black American women.<sup>51</sup> However, prospective studies have failed to confirm that douching causes PID<sup>52,53</sup> and it is likely that the vaginal discharge that is associated with PID may itself lead to increased douching.
- the oral contraceptive pill appears to reduce the risk of infection ascending into the upper genital tract and causing PID,<sup>54,55</sup> although the benefit may be limited to women with *C. trachomatis* infection and symptomatic PID.<sup>56</sup> The effect is probably mediated by progesterone-induced changes in the cervical mucous barrier and endometrial suppression, and/or a direct steroid effect reducing immune-related damage to the tubal mucosa.<sup>57,58</sup>
- use of non-progesterone IUD is associated with increased risk of PID but probably only for the initial few months after insertion<sup>59</sup> with the absolute risk thereafter being low. This risk can therefore be reduced considerably by appropriate screening and treatment of lower genital tract infections prior to IUD insertion.
- frequency of sexual intercourse in monogamous women,<sup>48</sup> although this may be limited to women with pre-existing bacterial vaginosis.<sup>60</sup>
- smoking increases the risk of PID by 1.7–2.3 fold<sup>61</sup> and, in one study, the more cigarettes smoked the higher the risk,<sup>62</sup> although the mechanism is unclear.

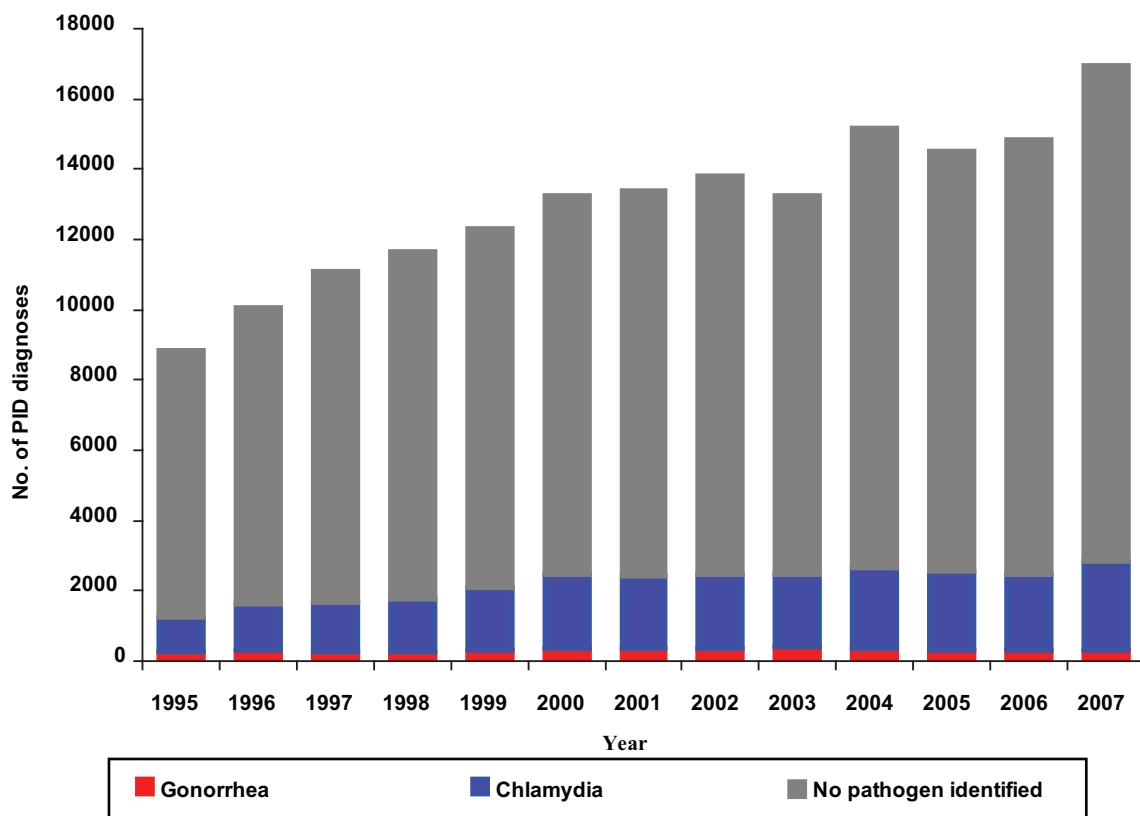


Fig. 45.1: Incidence of PID in genitourinary medicine clinics in England and Wales.

In addition, any operative procedure involving instrumentation of the cervical os has the potential to introduce infection into the upper genital tract, including termination of pregnancy,<sup>36</sup> hysterosalpingography, or *in vitro* fertilization.<sup>63,64</sup> Postpartum pelvic infection secondary to gonorrhea and chlamydia can occur and may be a particular problem in developing countries.<sup>65</sup>

Reported rates of PID in developing countries appear to be higher than in Western Europe and the US. In India and Pakistan, 9% to 19% of young women have been reported to have PID in community studies,<sup>66–68</sup> and the association with sexually transmitted diseases, such as gonorrhea and chlamydia, may be less strong in these countries.<sup>69,70</sup> A strong association has been noted with intrauterine contraceptive use<sup>67,68</sup> and access to care may also be a problem in some areas.<sup>66</sup> Elsewhere, rates of PID in gynecology inpatients vary from 7% in Egypt and 6% in Cuba to 17% to 40% in Africa, and 15% to 37% in Southeast Asia.<sup>71</sup> This is also reflected in high rates of infertility—approaching 50% in some areas of sub-Saharan Africa.<sup>71</sup>

## Pathology

PID is the result of organisms ascending from the mucosa of the vagina and cervix, via the endometrium, to the fallopian tubes and adnexae.<sup>15,72</sup> An active transport mechanism can move spermatozoa, dyes, and bacteria from the vagina to the upper genital tract<sup>73</sup> but it remains unclear what additional factors are required for PID to develop, although the loss of the cervical mucous plug during menstruation is probably also important. In addition, movement of bacteria to the upper genital tract may be facilitated by their attachment to either trichomonads or spermatozoa.

The endometritis associated with PID comprises a plasma cell infiltrate with polymorphonuclear cells and the formation of lymphoid follicles. In the upper genital tract, there is an initial acute inflammatory response, usually affecting both the fallopian tubes to some degree, with macroscopic swelling and erythema. An inflammatory exudate may build up within the fallopian tube, mixed with blood and necrotic epithelial cells, and lead to tubal obstruction. As subsequent healing occurs, adhesions form which can permanently block the tube, and chronic inflammation may result in a pyosalpinx or hydrosalpinx if the tube becomes blocked. Alternatively, the tube may remain patent but become chronically fibrosed and thickened with the invasion of mononuclear cells and formation of lymphoid follicles.

## CHLAMYDIA TRACHOMATIS

*C. trachomatis* invades both the ciliated and non-ciliated epithelial cells of the fallopian tube before replicating within an intracellular vacuole and releasing new infectious particles into the tube lumen.<sup>74</sup> Much of the inflammatory response to *C. trachomatis* is secondary to a delayed hypersensitivity reaction to a chlamydial heat shock protein rather than direct damage from bacterial invasion itself.<sup>75,76</sup> An associated Th1-type T cell

response initially occurs with the production of gamma interferon and interleukins 2, 6, and 10,<sup>77</sup> and histologically, a low-grade lymphocytic response is evident in the tissues.

## NEISSERIA GONORRHOEAE

Unlike *C. trachomatis*, *N. gonorrhoeae* initially primarily infects the non-ciliated cells with the production of tumor necrosis factor and gamma interferon, leading to collateral damage to the adjacent ciliated cells.<sup>78–80</sup> Following entry into epithelial cells, *N. gonorrhoeae* pass through the cytoplasm and basal cell surface to invade the submucosa<sup>81</sup> with an associated acute neutrophil response.

## Immunology

Re-infection with *N. gonorrhoeae* is frequently seen but some degree of strain-specific immune protection may occur, which reduces the risk of repeated upper genital tract involvement.<sup>8,82</sup> The intense immune-mediated response to upper genital tract infection seen with *N. gonorrhoeae* may be responsible for the decreasing isolation rates of the organism with increasing duration of symptoms.<sup>83</sup> This contrasts with recurrent infection with *C. trachomatis* where the immune response to infection is generally milder.<sup>4</sup> After priming by an initial episode of chlamydial PID, there is an increase in tubal damage if re-infection occurs,<sup>84</sup> possibly mediated by a cross-reaction between chlamydial heat shock protein 60 (hsp60) and human hsp60.<sup>85</sup>

## Clinical Features

PID may be symptomatic or asymptomatic and, even when present, clinical symptoms and signs lack sensitivity and specificity (the positive predictive value of a clinical diagnosis is 65% to 90% when compared to a laparoscopic diagnosis).<sup>6,86–88</sup> It also appears that some women with laparoscopic evidence of fallopian tube inflammation have symptoms, such as lower abdominal pain or intermenstrual bleeding, which are not initially recognized as being due to PID.<sup>89</sup>

The following features are suggestive of a diagnosis of PID, and the more features that are present the greater the likelihood of the diagnosis<sup>6,86,87,90</sup>:

- lower abdominal pain—usually bilateral and which may be worse on movement
- dyspareunia
- abnormal bleeding (irregular, heavy, or painful)—usually as a result of endometritis or cervicitis
- abnormal vaginal or cervical discharge
- lower abdominal tenderness, possibly with guarding
- adnexal tenderness on bimanual vaginal examination (high sensitivity but poor specificity<sup>91,92</sup>)—an inflammatory mass may be palpable (less sensitive but more specific<sup>91</sup>)
- cervical motion tenderness on bimanual vaginal examination (also known as cervical excitation)
- fever (>38°C)

- severe infection is associated with systemic symptoms such as malaise, fever, and vomiting.

It has been suggested that certain clinical criteria should be present in order for a diagnosis of PID to be made, e.g., abdominal tenderness plus cervical excitation plus adnexal tenderness. Although the presence of multiple clinical signs increases the likelihood of PID, the majority of cases are atypical or asymptomatic and a high index of suspicion is required since delayed treatment is associated with a higher rate of complications.<sup>93</sup> Gonococcal PID is associated with a shorter history of symptoms (<3 days) than chlamydial PID (>1 week)<sup>60</sup> and is clinically more severe<sup>4</sup> with a higher incidence of pyrexia and a palpable adnexal mass.<sup>4</sup>

The Fitz–Hugh–Curtis syndrome may complicate PID and comprises right upper quadrant pain and tenderness secondary to perihepatitis, which occurs in 10% to 20% of women with PID.<sup>94,95</sup> On examination, a hepatic friction rub is occasionally present. Sometimes, perihepatitis dominates the clinical picture and can be mistaken for acute cholecystitis. The Fitz–Hugh–Curtis syndrome may occur secondary to either chlamydial or gonococcal PID,<sup>96,97</sup> can be associated with abnormal liver function tests, and on laparoscopy, adhesions between the liver capsule and the overlying peritoneum are sometimes present.<sup>98</sup>

## Prognosis and Sequelae

Deaths due to PID are fortunately rare in industrialized countries<sup>99</sup> but short- and long-term complications are common. Untreated PID can progress rapidly (within days) to cause chronic inflammation, fibrosis, and tubal damage, resulting in chronic pain, infertility, and ectopic pregnancy. The risk of sequelae is increased with:

- delay in diagnosis and starting antibiotic therapy. Women waiting more than 3 days after the onset of abdominal pain have a three-fold increased risk of impaired fertility<sup>93</sup> which is most marked for chlamydial PID.
- severity of salpingitis as assessed at initial laparoscopy.<sup>43,100</sup>
- a second or subsequent episode of PID carries a much worse prognosis than the initial episode<sup>14,84,101,102</sup> (Fig. 45.2).
- not using the oral contraceptive, particularly for chlamydial PID.<sup>56</sup>
- non-gonococcal PID.<sup>84,103</sup>
- advanced age, in women with two or more episodes of PID.<sup>84</sup>

## TUBO-OVARIAN ABSCESS

Usually occurring as a late feature, abscess formation is associated with anaerobic infection.<sup>30,31</sup> Patients classically present with fever, malaise, and a tender adnexal mass, but clinical examination is unreliable. When the diagnosis is suspected, ultrasound scanning can be used to identify an abscess and assess the response to antibiotic treatment. If a rapid reduction in size is not evident over 72 hours or if the abscess is large (greater than 8-cm diameter), surgical drainage is usually required.

## CHRONIC PELVIC PAIN

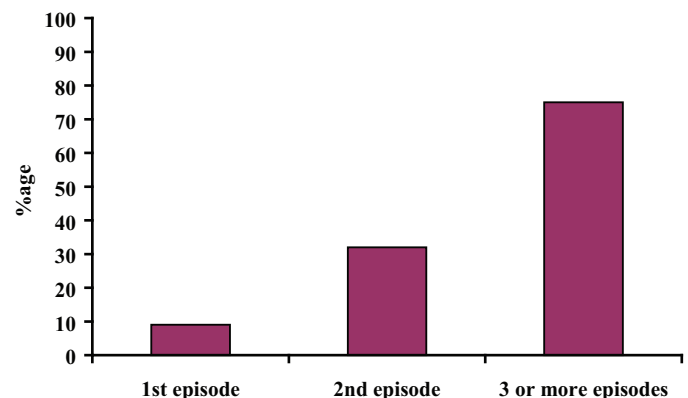
Adhesions can form within the pelvis following the acute inflammation of PID and are associated with symptoms of chronic pelvic pain, but severe pelvic pain can also occur in the absence of adhesions.<sup>104</sup> Chronic pelvic pain (lasting over 6 months) has been reported in 18% to 40% of women following PID.<sup>84,105–107</sup> Smaller series have found pelvic pain in more than half their patients<sup>39</sup> and the risk of chronic pain increases with the number of PID episodes. In developing countries, PID remains a common cause of pelvic pain—16% of cases in one series in Pakistan<sup>108</sup> and 31% in Mexico.<sup>109</sup>

Repeat courses of antibiotics are not helpful after the initial treatment of acute PID, suggesting that chronic pelvic infection is uncommon. Appropriate analgesia should be given and other pelvic pathologies excluded. Surgical intervention to divide adhesions is of limited value unless they are extensive,<sup>110</sup> but hysterectomy may be required for those with intractable pain.

## INFERTILITY

PID accounts for between a quarter and two-third of cases of infertility,<sup>111</sup> the higher proportion being seen in developing countries. The presence of antibodies to *C. trachomatis*, as a marker of past infection, is strongly associated with tubal infertility<sup>13</sup> but there is often no history of clinical PID suggesting that pelvic inflammation sufficiently severe to cause tubal damage often remains subclinical. The risk of infertility increases with each episode of PID—13% for an initial episode rising to 75% following 3 episodes of infection<sup>84</sup> (Fig. 45.2).

Surgical intervention to restore tubal patency has limited success possibly because the ciliated tubal epithelium, which plays an important role in transporting the ovum through the fallopian tube, remains damaged. *In vitro* fertilization provides an alternative when available. Although PID can reduce the chance of becoming pregnant, there is no subsequent increased risk of preterm delivery, stillbirth, or abortion.<sup>84</sup>



**Fig. 45.2:** Risk of infertility with tubal occlusion following PID.<sup>84</sup>



## ECTOPIC PREGNANCY

Chlamydial PID increases the relative risk of ectopic pregnancy by 2.4 to 7.9<sup>112,113</sup> with reported rates of 1% to 4%.<sup>84,106,114</sup> Some care needs to be taken in using ectopic pregnancy as a surrogate marker of PID prevalence because changes in IUD use, improved diagnosis, and an aging population of women attempting to get pregnant may all influence ectopic pregnancy rates.

## Diagnosis

As has already been highlighted, the clinical diagnosis of PID is insensitive and non-specific. Unfortunately, there is no “gold standard” test which will detect all cases of PID and a low threshold for starting antibiotic treatment is therefore required.

Laparoscopy may strongly support a diagnosis of PID<sup>32</sup> but is not justified routinely on the basis of cost, morbidity, and the potential difficulty in identifying mild intra-tubal inflammation or endometritis.<sup>6,32,86,87</sup> Laparoscopic findings are subjective and open to inter- and intra-observer variation—repeating the laparoscopy may detect abnormalities not visible at the initial procedure.<sup>6</sup> It may be particularly valuable in patients with systemic symptoms if the diagnosis is in doubt or if there is no response to antibiotics within 72 hours.

Ultrasound scanning may be useful to detect tubal abscesses<sup>115</sup> and transvaginal scanning may be sensitive enough to detect tubal changes associated with endometritis,<sup>116</sup> but diagnostic sensitivity will be dependent on the experience of the operator, and at present, routine use is not justified. Newer ultrasound techniques, including power Doppler imaging, may increase sensitivity by detecting the hyperemia associated with inflammation and permit the diagnosis of salpingitis.<sup>117</sup>

Endometritis is often associated with PID<sup>32</sup> and may correlate with its severity but endometrial inflammation is also frequently seen in women who have cervical infection without evidence of PID<sup>118</sup> and the distribution of changes in the endometrium may be patchy. The role of endometrial sampling in the diagnosis of PID is therefore unclear.

Laboratory markers may be of limited value—an elevated erythrocyte sedimentation rate or C-reactive protein support the diagnosis and correlate with the severity of PID<sup>119</sup> but are not specific to PID. An increase in the white blood count occurs in up to two-thirds of patients with PID but is also seen in many patients without PID, and tends to be within normal limits when PID is mild.<sup>88</sup> Culdocentesis (sampling from the pouch of Douglas) can be misleading since organisms present at this site are not necessarily also detectable from the fallopian tubes,<sup>120</sup> although an increased number of inflammatory cells in a culdocentesis sample does give some support to a diagnosis of PID.

## DIFFERENTIAL DIAGNOSIS

A number of other conditions need to be excluded in a young woman presenting with pelvic symptoms (Table 45.2).

**Table 45.2:** Main Differential Diagnosis of PID

Gynecological	Ectopic pregnancy
	Torsion/rupture/hemorrhage of ovarian cyst
	Endometriosis
Gastrointestinal	Appendicitis
	Irritable bowel syndrome
	Inflammatory bowel disease
Miscellaneous	Functional pain
	Pelvic adhesions secondary to previous pelvic pathology

## Ectopic Pregnancy

This is more likely if there is a history of amenorrhea followed by initial unilateral pain. It is advisable to perform a pregnancy test on all women with lower abdominal pain because of the severe consequences of a missed or delayed diagnosis of ectopic pregnancy. An ultrasound scan should be performed if the diagnosis remains in doubt.

## Bowel Pathology

Appendicitis is a relatively common cause of abdominal pain in young women. Classically, there is a history of central abdominal pain becoming localized to the right iliac fossa and associated with vomiting and diarrhea. Irritable bowel syndrome is also common in young women and inflammatory bowel disease can occur in this age group. The presence of colicky pain (which may be relieved on defecation), diarrhea, and/or constipation may suggest a gastrointestinal cause.

## Ovarian Pathology

Torsion, bleeding, or rupture of an ovarian cyst may result in pain and pelvic peritonism with a similar presentation to PID. A pelvic mass may be present and difficult to differentiate from a tubo-ovarian abscess. The onset of symptoms is usually unilateral, and more acute and severe than in patients with PID.

## Endometriosis

Endometriosis is less likely to cause fever than acute PID, and bacteriological cultures are usually negative, although both conditions can co-exist. The history is often chronic over many weeks or months and symptoms may be related to menstruation.

## Microbiology

Taking samples from the fallopian tubes, although desirable, is not usually practical but testing for gonorrhea and chlamydia in the lower genital tract is recommended since a positive result supports the diagnosis of PID. However, the absence of infection at this site does not exclude PID.<sup>6,86,87</sup>

Appropriate screening tests include:

- endocervical and urethral microscopy and culture for gonorrhea—samples should also be taken from the rectum and throat if the history indicates that these sites may have been exposed to infection. Increasingly nucleic acid amplification tests (NAATs) are providing an alternative to gonococcal culture and can be performed on non-invasive samples such as self-taken vulval swabs.
- endocervical samples for NAAT chlamydia tests (culture and enzyme-linked immunoassay testing are significantly less sensitive)—urine or vulval swabs can also be used with NAAT chlamydia tests.
- consider screening for other sexually acquired infections such as trichomoniasis, syphilis, HIV, chancroid, and lymphogranuloma venereum, depending on the local prevalence, clinical history, and availability of laboratory tests.

## Serology

Up to 59% of women with chlamydial PID will develop an antibody response and higher antibody levels may be associated with more severe disease,<sup>121</sup> but lack of specificity (in particular cross-reaction with *C. pneumoniae*) and the delay in the appearance of antibodies limit the usefulness of serology in making a diagnosis.

## Treatment

Broad-spectrum antibiotic therapy is required to cover *N. gonorrhoeae*, *C. trachomatis*, and anaerobic infection.<sup>6,86,122</sup> Good-quality evidence of the long-term effectiveness of therapy in preventing the complications of PID is currently lacking and there are comparatively fewer data on oral than parenteral regimens. The choice of an appropriate treatment regimen may be influenced by:

- Knowledge of local antimicrobial sensitivity patterns

Antibiotic resistance is very unlikely for *C. trachomatis* but knowledge of local patterns of resistance to *N. gonorrhoeae* may guide the initial choice of therapy. If more than 5% of local isolates are resistant, then the choice of empirical antibiotics should be reviewed.

- Cost

There is little evidence that any one of the regimens recommended below has superior efficacy compared to the others; therefore, it may be appropriate for cost to influence the choice of antibiotics.

- Patient factors

Choosing a regimen with once or twice daily dosing, small pill burden, and few side-effects to improve acceptability and adherence is of particular relevance for outpatient therapy. A history of allergy,

renal or hepatic impairment, and interactions with other concurrent therapy may influence the choice of antibiotics.

- Severity of disease

For patients who have more severe systemic manifestations of PID parenteral therapy as an inpatient may achieve higher tissue levels of antibiotics and permit close monitoring. It remains unclear if it improves the prospect of preserving fertility.

- General advice

Rest is advised for those with severe disease and appropriate analgesia should be provided. If there is a possibility that the patient could be pregnant, a pregnancy test should be performed.

Patients should be advised to avoid unprotected intercourse until they, and their partner(s), have completed treatment and follow-up, and all patients should be offered screening for other sexually transmitted infections. A detailed explanation of their condition with particular emphasis on the long-term implications for their health and of their partner(s) should be provided, reinforced with clear and accurate written information.

## CRITERIA FOR INPATIENT MANAGEMENT

Admission for parenteral therapy, observation, further investigation, and/or possible surgical intervention should be considered in the following situations<sup>86,123</sup>:

- severe symptoms or signs
- presence of a tubo-ovarian abscess
- pregnancy
- inability to tolerate an oral regimen
- lack of response or intolerance to oral therapy

## TREATMENT REGIMENS

Evidence-based antibiotic regimens are available but direct comparisons of different treatments need to be interpreted with caution since there is little standardization between clinical trials for assessing diagnosis and measuring outcomes. It is recommended that for inpatient management, intravenous therapy should be continued until 24 hours after clinical improvement and then switched to oral. Dosage recommendations may need to be adjusted slightly, depending on local licensing regulations and the availability of drug formulations.

## Outpatient Regimens

- Oral ofloxacin 400 mg twice daily plus oral metronidazole\* 500 mg twice daily for 14 days.<sup>100,124–127</sup> A single dose of IM ceftriaxone 250 mg should be added in areas with a high prevalence of quinolone-resistant *N. gonorrhoeae*.
- IM ceftriaxone 250 mg single dose (or IM cefoxitin 2 g single dose with oral probenecid 1 g) followed by oral doxycycline 100 mg twice daily plus metronidazole\* 400 mg twice daily for 14 days.<sup>122</sup>

\*Metronidazole may be omitted if patients have clinically mild disease (with less likelihood of anaerobic infection) and are suffering from gastrointestinal side effects.

- Oral moxifloxacin 400 mg once daily for 14 days.<sup>128,129</sup> A single dose of IM ceftriaxone 250 mg should be added in areas with a high prevalence of quinolone-resistant *N. gonorrhoeae*.

## Inpatient Regimens

- Intravenous cefoxitin 2 g four times daily (or IV cefotetan 2 g twice daily) plus IV doxycycline 100 mg twice daily (oral doxycycline may be used if tolerated or if IV doxycycline is not available) followed by oral doxycycline 100 mg twice daily plus oral metronidazole 400 mg twice daily for a total of 14 days.<sup>86,122,124,130,131</sup>
- Intravenous clindamycin 900 mg three times daily plus IV gentamicin (2 mg/kg loading dose followed by 1.5 mg/kg three times daily [a single daily dose may be substituted]) followed by either oral clindamycin 450 mg four times daily or oral doxycycline 100 mg twice daily plus oral metronidazole 400 mg twice daily to complete 14 days.<sup>86,122,130,131</sup>
- Intravenous ofloxacin 400 mg twice daily plus IV metronidazole 500 mg three times daily for 14 days.<sup>86,124,130</sup> IV cefoxitin 2 g four times daily should be added in areas with a high prevalence of quinolone-resistant *N. gonorrhoeae*.
- Intravenous ciprofloxacin 200 mg twice daily plus IV (or oral) doxycycline 100 mg twice daily plus IV metronidazole 500 mg three times daily.<sup>86,124,132</sup> IV cefoxitin 2 g four times daily should be added in areas with a high prevalence of quinolone-resistant *N. gonorrhoeae*.

Where the above regimens are not available, antibiotic therapy should be given for 14 days in an attempt to cover:

- *Neisseria gonorrhoeae*, e.g., cephalosporins, quinolones (if locally sensitive), penicillin (if locally sensitive).
- *Chlamydia trachomatis*, e.g., tetracyclines, macrolides.
- anaerobic bacteria, e.g., metronidazole.

Review at 72 hours is recommended,<sup>86</sup> particularly for those with a moderate or severe clinical presentation, and should show a substantial improvement in clinical symptoms and signs. Failure to do so suggests the need for further investigation, parenteral therapy, and/or surgical intervention.

## ACTINOMYCES-ASSOCIATED PID

Pelvic actinomycosis is extremely rare but actinomyces organisms may be found in the female genital tract as a commensal, particularly in women with an IUD.

For women who have actinomyces-like organisms identified on a cervical smear when an IUD is *in situ*, the following approach is suggested<sup>133</sup>:

- if asymptomatic, the IUD may be left in place and the woman advised to return if symptoms occur.
- if symptomatic, the IUD should be removed and sent for culture of actinomyces (a cervical swab is not an appropriate specimen to detect actinomyces infection). No further treatment is generally required and an IUD may be reinserted if required.

If treatment is required in a persistently symptomatic woman, then amoxicillin 3 g daily in divided doses for at least 14 days combined with metronidazole can be used.

## MANAGEMENT OF PARTNERS

The current male partners of women with PID should be contacted and offered health advice and screening for gonorrhea and chlamydia. Other recent sexual partners may also be offered screening with contacts over a 6-month period being sought, although this time period may be influenced by the sexual history. Partners identified in this way should be advised to avoid intercourse until they and the index patient both have completed a course of treatment. Gonorrhea diagnosed in the male partner should be treated appropriately and concurrently with the index patient. Concurrent empirical treatment for chlamydia is recommended for all sexual contacts due to the variable sensitivity of currently available diagnostic tests. If adequate screening for gonorrhea and chlamydia in the sexual partner(s) is not possible, empirical therapy for gonorrhea and chlamydia should be given.

A further review 4 weeks after therapy may be useful to ensure:

- an adequate clinical response to treatment.
- a full course of antibiotics was completed.
- all relevant sexual contacts have been approached for screening and treatment.

Repeat testing for gonorrhea and chlamydia may be appropriate in those in whom persisting symptoms, compliance with antibiotics, antibiotic resistance pattern, and/or tracing of sexual contacts indicate the possibility of persisting or recurrent infection.

## SPECIAL SITUATIONS

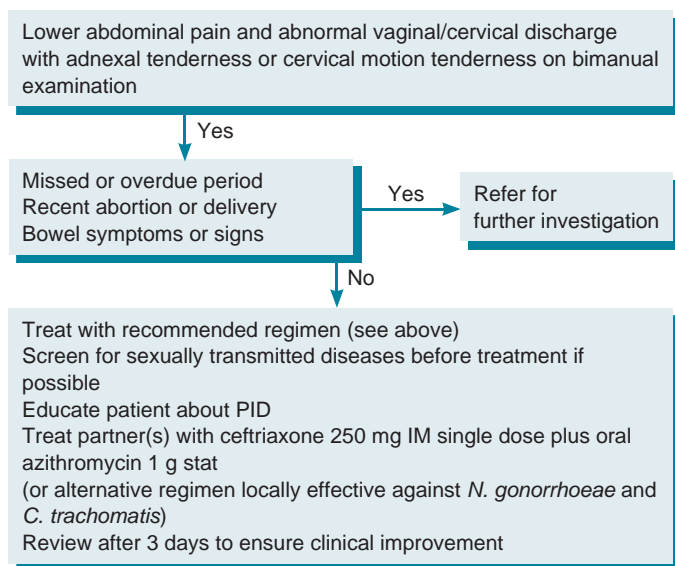
### Intrauterine Device

Two retrospective studies<sup>134,135</sup> and a small prospective clinical trial<sup>136</sup> have shown no difference in short-term outcomes following removal of an IUD in women with PID, but a more recent large prospective trial has reported a significant clinical benefit when the IUD is removed.<sup>137</sup> A small number of fatalities have also been associated with IUD use.<sup>138</sup> Removal of the IUD should therefore be considered, especially in women with moderate-to-severe disease. The prophylactic use of antibiotics to prevent the introduction of infection into the upper genital tract during IUD insertion has not been found to be effective.<sup>139</sup>

## SYNDROMIC MANAGEMENT

When medical support services are limited, a syndromic approach to management may be required. Figure 45.3 summarizes how such a patient should be managed.





**Fig. 45.3:** Syndromic management of PID.

## Prevention

### PRIMARY PREVENTION

Screening high-risk women for chlamydia infection and providing appropriate treatment are associated with a reduction in PID of more than 50% women.<sup>140</sup> The use of barrier contraception can also be effective and reduces the risk of PID by about 40%.<sup>141</sup>

In women undergoing surgical procedures that increase the risk of introducing infection into the upper genital tract, antibiotic prophylaxis should be considered if screening for sexually transmitted infections has not been performed, e.g., termination of pregnancy, hysterosalpingography, dilatation, and curettage. There is little data on which to base the choice of which antibiotics to use but cover for *N. gonorrhoeae*, *C. trachomatis*, and anaerobes, based on local sensitivity patterns, is desirable.

### SECONDARY PREVENTION

Since the risk of sequel is significantly higher with recurrent PID, appropriate health education, tracing of sexual contacts, and screening of those at risk are desirable.

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## Introduction

The term “mycoplasmas” is commonly used as the trivial name for members of the class Mollicutes (from Greek *mollis*, soft; *cutis*, skin, i.e., the “soft-skinned”). They are the smallest free-living bacteria but lack the rigid cell wall of other bacteria, making them resistant to penicillins and related antimicrobials. Instead, they have a flexible trilaminar unit membrane enclosing the cytoplasm. Mycoplasmas are usually 0.4–0.5  $\mu$  but viable cells, even smaller than 0.3  $\mu$ , are not unusual. The small size and flexible membrane enable them to pass through filters with pore-sizes as small as 0.2  $\mu$ , which are generally believed to retain all bacteria. The filterability and lack of formation of a cell wall after incubation in medium without antibiotics has now become one of the key properties defining new species as mycoplasmas.<sup>1,2</sup> The mycoplasmas isolated commonly from humans belong to the order Mycoplasmatales and family Mycoplasmataceae containing two genera: *Mycoplasma* and *Ureaplasma*. The genus *Mycoplasma* contains more than 100 species, of which 16 at present are considered a part of the human flora. *M. hominis* and *M. genitalium* are the two mycoplasma species most often found in the urogenital tract. Two ureaplasma species *U. urealyticum* and *U. parvum* (previously known as *U. urealyticum*, parvo biovar) are commonly found in the human urogenital tract. Ureaplasmas uniquely hydrolyze urea and were originally termed T-strains or T-mycoplasmas because of the tiny (T) colonies (15–60  $\mu$ m diameter) they form on agar medium,<sup>3</sup> in contrast to the larger (90  $\mu$ m or more diameter) characteristic ‘fried-egg’-like colonies produced by most other mycoplasmas.

The small size of the mycoplasma genome (as little as 580 kbp for *M. genitalium*<sup>4</sup>) restricts metabolic capabilities, making culture of some mycoplasmas difficult or impossible. Despite their general similarity, mycoplasmas form a heterogeneous group with differing host specificities, nutritional requirements, metabolic reactions, and DNA and antigenic composition. They are believed to have evolved from gram-positive bacteria most closely related to the clostridia by degenerative evolution leading to genomic reduction.<sup>5</sup> Mycoplasmas, particularly species with the smallest genomes, have high mutation rates, suggesting that they are in a state of rapid evolution.<sup>6</sup>

Most mycoplasma genomes have a low guanine plus cytosine (G+C) content, within the range of 24–33% G+C. Mycoplasmas are difficult to study by classical genetic tools, both because of their fastidious growth requirements, and as a consequence of the absence of selectable markers. Furthermore, in contrast to other bacteria but similar to mitochondria, *Mycoplasma* use the UGA codon to code for tryptophan instead of the common STOP signal. This means that expression of mycoplasma genes in common bacterial systems is complicated due to the synthesis of truncated proteins.

In this chapter, the designation ureaplasmas will be used where the species has not been determined or where it is irrelevant. Apart from ureaplasmas, *M. hominis*, and *M. genitalium*, *M. fermentans*, *M. penetrans*, *M. primatum*, and *M. spermatophilum* are believed to primarily reside in the urogenital tract. However, as the detection rate of the latter four is generally low, and as their pathogenic potential is not determined, these species will not be discussed in more detail here.

## Epidemiology

### COLONIZATION OF INFANTS AND CHILDREN

Infants may become colonized with genital mycoplasmas during passage through the birth canal; infants who are delivered by caesarean section are colonized less often than those delivered vaginally,<sup>7</sup> but intrauterine transmission also occurs.<sup>8</sup> Ureaplasmas and *M. hominis* may be transmitted to about 40% of babies born to infected mothers<sup>9</sup> and have been isolated from the genitalia or respiratory tract of up to one-third of infant girls. Boys are less frequently colonized and tend to clear the colonization earlier.<sup>7,10</sup> Genital mycoplasmas are rarely recovered from urine or genital-tract specimens from prepubertal boys, and in <10% of prepubertal girls. In sexually abused children, figures of as much as 48% and 34%, respectively, have been recorded.<sup>11</sup> Since *M. genitalium* can be detected in the cervix, vagina, and endometrium, the potential for neonatal infection exists. However, in most populations of pregnant women, the detection rate is well below 5%<sup>12</sup> and only a single case of detection of *M. genitalium* in a neonate has been reported to date.<sup>13</sup>

## COLONIZATION OF ADULTS

In adults, the colonization rate with *M. hominis*, *M. genitalium*, and ureaplasmas increases proportionally with the number of different sexual partners.<sup>14–17</sup> Ureaplasmas can be found in the cervix or vagina of 40–80% of sexually active, asymptomatic women, and *M. hominis* in 20–50%. The colonization rate is somewhat lower in the urethra of healthy males. In women, colonization is strongly linked to bacterial vaginosis (BV); a fact that has led to much confusion in the interpretation of their role in diseases where BV is a risk factor. In contrast to the very frequent detection of ureaplasmas and *M. hominis*, *M. genitalium* is found in only 1–3% of sexually active men and women in population based studies,<sup>16,17</sup> whereas it can be detected in about 5% of asymptomatic sexually transmitted disease (STD)-clinic attendees.<sup>18</sup>

## Clinical Manifestations and Sequelae

Ureaplasmas and *M. hominis* are very frequently isolated from the lower genital tract of healthy individuals. Probably, the organisms only reach the upper tract in a subpopulation of individuals infected in the lower urogenital tract, and disease may only develop in some of the individuals with ascending infection. Consequently, in most cases, they should primarily be considered as commensals when detected in the lower genital tract. However, these mycoplasmas are recognized as common causes of extragenital disease in immunocompromised patients and in newborn infants, particularly preterm infants. In contrast, the link between detection of *M. genitalium* and disease is much stronger.

## Disease in Men

### NONGONOCOCCAL URETHRITIS

*M. genitalium* has been strongly and uniformly associated with nongonococcal urethritis (NGU) in more than 30 studies, and has been detected in the urethra of 15–25% of men with symptomatic NGU compared to about 5–10% of those without this disease.<sup>19</sup> In those studies where the association with nonchlamydial NGU (NCNGU) was evaluated, the association has generally been stronger, suggesting that *M. genitalium* and *C. trachomatis* may act as separate causes of the condition. In several studies, *M. genitalium* has been found in more than one-third of men with NCNGU.<sup>20–24</sup> Among STD clinic populations, approximately 90% of *M. genitalium*-infected men have microscopic evidence of urethritis and almost three-fourths report symptoms.<sup>25–28</sup> Quantitative PCR assays for *M. genitalium* has shown a dose/response relationship between signs and symptoms of urethritis and *M. genitalium* DNA load in urethral and urine specimens, further supporting the causal relationship of *M. genitalium* with urethritis.<sup>29,30</sup> Finally, animal experiments have demonstrated that intraurethral inoculation of male primates with *M. genitalium* results in the development of urethritis, shown most impressively in chimpanzees with shedding of the organism for up to 18 weeks after inoculation and transmission of the organism from infected

to uninfected chimpanzees. Furthermore, an antibody response could be detected in most of the chimpanzees; thus, fulfilling Koch's postulates of causation.<sup>31,32</sup>

Several clinical studies have shown a strong correlation between *M. genitalium* and persistent or recurrent NGU, probably due to the poor microbiologic treatment efficacy of tetracyclines. *M. genitalium* has generally been eradicated from less than 1/3 of the infected patients after treatment with standard doses of tetracyclines.<sup>33–35</sup> *M. genitalium* has been found in as many as 41% of men with persistent or recurrent urethritis after treatment with doxycycline.<sup>36–38</sup> More recently, azithromycin treatment failure after a 1 g single dose was reported among 28% of men with *M. genitalium*-positive NGU and was correlated with macrolide resistance developing during treatment with a single dose in most patients.<sup>39</sup>

In contrast to the consistency of studies associating *M. genitalium* with NGU, the role of the ureaplasmas in this disease has been more controversial. The results of human<sup>40,41</sup> and animal inoculation studies,<sup>42</sup> together with those of controlled antibiotic and serologic investigations, support a causal role for ureaplasmas in NGU, particularly chronic disease,<sup>36,43</sup> although they lag behind *Chlamydia trachomatis* and *M. genitalium* in importance. Obviously, demonstrating ureaplasmas in a man with NGU does not necessarily indicate that this organism is the cause of the disease considering the high colonization rate. Thus, the exact proportion of cases for which ureaplasmas are responsible is difficult to establish. The division of the human ureaplasmas into two species, *U. urealyticum* and *U. parvum*, respectively,<sup>44</sup> led to studies aiming at showing that one of the species was primarily causing disease whereas the other was a commensal.<sup>45–47</sup> *U. parvum* was isolated more often from the control group indicating that this species has a lower pathogenic potential. However, the role of *U. urealyticum* is still uncertain as one study showed an association between this species and NGU<sup>46</sup> whereas another did not.<sup>47</sup> The third study showed an association when crude data was analyzed, whereas only young age was associated with *U. urealyticum* when a logistic regression analysis was applied.<sup>45</sup> Furthermore, in only a few studies has there been control for infection with *C. trachomatis* or *M. genitalium*. Predisposing factors, such as a lack of mucosal immunity in individuals who develop disease, are likely to play a significant role as indicated by a single study where repeated inoculation of a human subject led to a gradual decrease of the inflammatory response.<sup>48</sup> Some patients with hypogammaglobulinemia develop a prolonged urethritis with persistent ureaplasma infection.<sup>49</sup> In such cases, treatment is often complicated by antimicrobial resistance and a combination of different classes of antibiotics is recommended.

There is no evidence supporting a role for *M. hominis* as a cause of urethritis.<sup>27,50</sup>

### PROSTATITIS

A number of studies reported the isolation of ureaplasmas from expressed prostatic secretions obtained after prostatic massage



more often and in greater numbers in men with chronic prostatitis than in controls.<sup>51,52</sup> However, unequivocal evidence for a causal role in acute disease does not exist. *M. genitalium* has been detected by PCR technology in prostatic biopsies from 5 of 135 men and in semen from 2 of 18 men with chronic abacterial inflammatory prostatitis compared to none of 20 controls.<sup>53</sup> However, further studies are needed to confirm these findings. Ureaplasmas have not been found in prostatic biopsies from patients with chronic abacterial prostatitis,<sup>54</sup> and *M. hominis* has not been associated with prostatitis of any kind in most studies.

## EPIDIDYMITIS

Ureaplasmas have been recovered from the urethra and directly from epididymal aspirate fluid, accompanied by a specific antibody response, in a patient with acute nongonococcal, nonchlamydial epididymitis.<sup>55</sup> Clinical experience as well as the detection of *M. genitalium* in a few patients during a treatment trial<sup>56</sup> indicate that *M. genitalium* may be a cause of acute epididymitis. However, further studies are required to establish a causal role.

## Disease in Women

### BACTERIAL VAGINOSIS

Bacterial vaginosis (BV) is one of the most common genital infections among women of reproductive age<sup>57</sup> affecting 5–25% of all women. However, its etiology is largely unknown. BV is characterized by a disturbance of normal vaginal flora, with a loss of hydrogen peroxide-producing *Lactobacillus* species and an increase in gram-variable coccobacilli, anaerobic organisms, as well as *M. hominis* and, to a lesser extent, ureaplasmas.<sup>58,59</sup> Both ureaplasmas and *M. hominis* are found in higher numbers in the vagina of women who have BV than in healthy women.<sup>60</sup> However, since the mycoplasmas exist with a variety of other bacteria, also in large numbers, their role in the symptoms and sequelae of BV is not clear. Notably, the mycoplasmas seem to disappear after successful treatment of BV with metronidazole, which has no activity against mollicutes.<sup>61</sup> *M. genitalium* does not seem to be associated etiologically with BV,<sup>59,62</sup> although in some studies it has been detected more frequently in women with BV than in those without.<sup>63</sup>

The strong association between ureaplasmas, *M. hominis*, and BV raises significant problems in determining the roles of these two bacteria in female genital tract infections as BV is a strong predictor of infectious complications in women and as BV has not regularly been controlled for in studies of urogenital mycoplasmas.

### CERVICITIS

One of the major problems in interpreting studies on the association between urogenital mycoplasmas and cervicitis is the lack of a uniform definition of cervicitis. Some studies consider the presence of 10 polymorphonuclear leukocytes (PMNLs) in a cervical smear significant, whereas others demand 30 PMNLs/

hpf to define cervicitis. Also, vaginal leukocytosis (i.e., more PMNLs than epithelial cells in a vaginal wet smear) or the presence of macroscopic cervical mucopus is commonly used and the specificity of these signs has not been thoroughly validated.

In most, but not all studies, *M. genitalium* has been associated with cervicitis. Several studies, however, failed to show significant differences and in general, the association is much weaker than that between *M. genitalium* and male urethritis. In an early study by Uno et al., *M. genitalium* was detected in 8% of women with cervicitis as compared to none of 80 asymptomatic pregnant women.<sup>64</sup> Manhart et al. found *M. genitalium* in 11% of women with cervicitis ( $\geq 30$  PMNLs/hpf) and in 5% of women without cervicitis. In a multivariate logistic regression analysis *M. genitalium* remained strongly associated with cervicitis (OR 3.1; 95% CI 1.5–6.8), supporting an independent role for *M. genitalium* as a cause of cervicitis.<sup>62</sup> In a study from Sweden, *M. genitalium* was significantly associated with cervicitis defined as  $\geq 30$  PMNLs/hpf, since 12% of 85 women with cervicitis were *M. genitalium* PCR positive as compared to 5% of 356 without.<sup>26</sup> In contrast, Casin et al. were unable to demonstrate any correlation between the presence of *M. genitalium* and clinical, demographic, or microbiologic data in women with genital symptoms attending an STD clinic in Paris.<sup>65</sup>

In studies where signs of urethritis have been recorded, female urethritis has been significantly associated with *M. genitalium* infection.<sup>26,66</sup>

The role of ureaplasmas and *M. hominis* in cervicitis has not been studied in great detail. Mucopurulent cervicitis has been associated with isolation of ureaplasmas,<sup>67</sup> although the role of bacterial vaginosis as a confounder was not assessed.

### PID AND SEQUELAE

Pelvic inflammatory disease (PID) is caused by microbes in the vagina and cervix ascending and invading the upper genital tract. *C. trachomatis* and *N. gonorrhoeae*, are the best established etiological agents, but the mixed bacterial flora associated with BV has also been implicated as a cause of this condition,<sup>68</sup> and the role of ureaplasmas and *M. hominis* should be considered in that context. In contrast, *M. genitalium* appear to be independent of BV.

*M. hominis* has been recovered more frequently from vaginal and cervical specimens from women with PID than from healthy women.<sup>69,70</sup> However, since *M. hominis* is very closely associated with BV, and since studies linking *M. hominis* to PID did not include an assessment of BV, the data are difficult to interpret. *M. hominis* has been isolated apparently in pure culture from the fallopian tubes of women with salpingitis diagnosed by laparoscopy, but not from women without lesions.<sup>71</sup> In several studies, a 4-fold rise in antibody titer to *M. hominis* has been found more often among women who had PID than among controls, but no control for BV was reported.<sup>69,72</sup> Damage to fallopian tube epithelium has been studied in organ cultures and it was demonstrated that *M. hominis* multiplied and persisted but caused negligible damage.<sup>73</sup>

Although ureaplasmas have also been isolated occasionally directly from the fallopian tubes of patients with PID,<sup>74,75</sup> they have usually been found in association with other known pathogens and are not thought to play a major role.

*M. genitalium* has been detected in the endometrium of 60% of those positive in the cervix, and its presence in endometrial biopsies has been strongly associated with histological endometritis and with recurrent PID.<sup>76,77</sup> This probably reflects the poor effect of doxycycline used as first-line treatment. Tubal scarring has been indirectly linked with *M. genitalium* infection by a significantly higher proportion of women with tubal factor infertility having antibodies against the bacterium compared to women with infertility from other causes.<sup>78</sup> Although antibodies against *M. genitalium* have been found twice as often in younger women with ectopic pregnancy as compared to pregnant controls in one study, the difference was not statistically different.<sup>79</sup> In a single small study, *M. genitalium* was found by PCR more often in idiopathic infertility than in controls.<sup>80</sup> It would be expected, however, that the effect of PID leading to occluded tubes would be better demonstrated by serology than by PCR technology since the infection may have been present long before infertility became apparent. On the other hand, infertility could also be an effect of endometritis, a condition quite strongly associated with *M. genitalium* infection.

*M. genitalium* has been detected by PCR in a few laparoscopically obtained fallopian tube specimens from women with salpingitis,<sup>81</sup> and causes lower genital tract inflammation in chimpanzees<sup>32</sup> as well as salpingitis in marmosets, grivet monkeys, and baboons.<sup>82</sup> Its ability to attach to spermatozoa may mediate the ascension into the upper genital tract.<sup>83</sup>

In conclusion, there is some evidence that *M. hominis* may be a cause of PID, possibly as part of the BV associated flora but there is very little evidence that ureaplasmas have a similar role. *M. genitalium* is not associated with bacterial vaginosis, but there is increasing evidence that it may play a causal role in cervicitis, endometritis, and PID.

## Urinary Tract Disease

### PYELONEPHRITIS AND UTI

*M. hominis* does not appear to play an important role in acute cystitis.<sup>84</sup> However, ureaplasmas have been associated with symptoms of cystitis and with the acute urethral syndrome in women without significant bacteriuria, and have been isolated from up to 25% of suprapubic aspirates from such women.<sup>85,86</sup> No studies have assessed the importance of *M. genitalium* in these conditions although it has been clearly associated with urethral inflammation.<sup>26,66</sup>

Despite the lack of evidence for *M. hominis* causing acute cystitis, it is thought to be involved in up to 10% of cases of acute pyelonephritis.<sup>87</sup> Antibodies in isolation-positive patients were also demonstrated in a high proportion of cases.<sup>88</sup> There is no evidence suggesting a similar role for ureaplasmas, and *M. genitalium* has not been studied. Surprisingly, no systematic studies have been conducted for more than 30 years despite the apparent importance of the observation and the treatment implications.

### URINARY CALCULI

Infection stones may be caused by urea-hydrolyzing bacteria, including *Proteus* and ureaplasmas. These stones are composed of magnesium ammonium phosphate (struvite) and carbonate-apatite and ureaplasmas have been detected in 12–27% of infection stones,<sup>89,90</sup> occasionally in pure culture, and more often in the urine and stones of patients with infection stones, compared to those with metabolic stones.<sup>91</sup> However, the true impact of ureaplasmas in the development of renal calculi remains to be determined.

## Effects of Genital Mycoplasmas on Pregnancy

### INFERTILITY

Although ureaplasmas and *M. hominis* have been associated with both male-factor and female-factor infertility in some studies, no convincing evidence has been obtained.

### ADVERSE PREGNANCY OUTCOME

Studies based on the detection of ureaplasmas and *M. hominis* from the endometrium or placenta have shown a more consistent association with spontaneous abortion than have studies where the mycoplasmas have been sought only in lower genital tract specimens, but whether the organisms are responsible is unclear. However, the strong link between BV and *M. hominis* in particular should always be borne in mind, since BV has been associated with both preterm labor and stillbirth.<sup>92</sup>

Ureaplasmas have been isolated more frequently from spontaneously aborted fetuses and stillborn or premature infants than from induced abortions or normal full-term infants. Ureaplasmas have been isolated from the lungs and from the brain, heart, and viscera suggesting that it was not just superficial contamination.<sup>93,94</sup> Whether the invasion occurred before or after the fetal death, however, is not clear.

Chorioamnionitis and mycoplasmal infection have been shown to be significantly associated, even when corrected for the duration of membrane rupture.<sup>95–97</sup> Both ureaplasmas and *M. hominis* can invade the amniotic sac before 20 weeks of gestation in the presence of intact fetal membranes and apparently in the absence of other microorganisms.<sup>97</sup> Detection in mid-trimester amniotic fluid has been associated with preterm premature rupture of the membranes with subsequent preterm birth.<sup>98,99</sup> However, not all infected women delivered preterm.

Isolation of ureaplasmas from the placenta is significantly associated with histologic chorioamnionitis and funisitis, stillbirth, and perinatal morbidity and mortality.<sup>100,101</sup>

The isolation of *M. hominis* from amniotic fluid is almost always associated with clinical symptoms (maternal fever, uterine tenderness, foul vaginal discharge). Ureaplasmas, on the other hand, have been known to persist in amniotic fluid for as long as 2 months, in the presence of an intense inflammatory response, sometimes without clinical signs or symptoms of amnionitis.<sup>97</sup>

*M. genitalium* has been associated with preterm birth in a few studies,<sup>102,103</sup> but not in others.<sup>12,104,105</sup> It is usually found at a low prevalence in pregnant women and as such, is probably relatively unimportant during pregnancy.

## NEONATAL INFECTIONS

Ureaplasmas can be isolated from the respiratory tract of neonates. The isolation rate appears to correlate strongly with birth-weight as infants of very low birth-weight (under 1000 g) are infected much more often than full-term infants.<sup>106</sup> A meta-analysis has shown that ureaplasma colonization of the lower respiratory tract of infants <1500 g increases the risk of development of chronic lung disease.<sup>107</sup> *M. hominis* has very rarely been implicated in pneumonia soon after birth, but both *M. hominis* and ureaplasmas have been isolated from the cerebrospinal fluid of neonates with meningitis or brain abscess and should be considered in culture negative neonatal meningitis.<sup>108</sup>

## BLOODSTREAM INFECTION

Ureaplasmas and *M. hominis* can contribute significantly to bloodstream infections in an obstetric and gynecological setting each accounting for almost 10% of positive cultures.<sup>109</sup> When *M. hominis* has been isolated from the blood, an antibody response can be almost uniformly demonstrated.<sup>110,111</sup> While *M. hominis* and ureaplasmas are not highly pathogenic and many patients recover spontaneously, the infections contribute to increased length of hospital stay and costs associated with the investigation of fever postpartum or postoperatively.

It is important to realize that most commercially available blood culture media contain sodium polyanethol sulfonate (SPS), which inhibits the growth of mycoplasmas<sup>112</sup>; consequently, special media should be employed when mycoplasma infection is suspected.

## SEXUALLY ACQUIRED REACTIVE ARTHRITIS

Arthritis occasionally develops concomitantly with or shortly after NGU. This is generally referred to as sexually acquired reactive arthritis (SARA). If the SARA is associated with conjunctivitis and urethritis, the condition is referred to as Reiter syndrome. *M. genitalium* has been detected in the synovial fluid of a patient with SARA<sup>113</sup> and clinical experience has shown that SARA is not uncommon after *M. genitalium*-positive NGU, but no systematic studies have been presented. The evidence for a role of ureaplasmas in SARA is mainly indirect and based on a specific response of synovial mononuclear cells to antigens from ureaplasmas.<sup>114</sup>

## Mycoplasma Infections in Immunodeficient Patients

Patients with antibody deficiencies, such as hypo- or agammaglobulinemia, are particularly susceptible to extragenital mycoplasma infections. *M. hominis* and ureaplasmas have been found in septic arthritis, osteomyelitis, subcutaneous abscesses, and cellulitis.<sup>115</sup> Cystitis and chronic urethritis is common and it is

often very difficult to eradicate the mycoplasmas.<sup>116,117</sup> Prolonged intravenous and combination therapy with increased dosages of antibiotics should be considered to avoid antimicrobial resistance developing due to suboptimal drug concentrations at the infection site, and the gammaglobulin dosage should be increased. In general fluoroquinolones with extended gram-positive spectrum such as moxifloxacin are recommended due to their bactericidal effect and potency against a broad spectrum of mollicutes but always in combination with another antibiotic class such as tetracyclines.

## Diagnosis

*M. hominis* and ureaplasmas are found so commonly in the lower genital tract of healthy men and women that the mere detection of these species should be interpreted cautiously. In contrast, *M. genitalium* is less frequently detected in healthy individuals, and detection should in general lead to treatment. In most situations, swabs from the urethra or cervix/vagina provide a slightly better specimen for mycoplasmal detection than urine specimens. Ureaplasmas and *M. hominis* usually show evidence of growth in special culture media within 1 to 5 days. Primary isolation of *M. genitalium* is difficult and may take 50 days or more, and consequently, PCR is used to detect this species. PCR assays for detection of *M. hominis*, *M. fermentans*, *M. pirum*, *M. penetrans*, and *U. urealyticum/U. parvum* are also available in some laboratories. Mycoplasmas are fastidious and demanding in their requirements for special media. Commercially available media may be useful but are often significantly less sensitive than media produced in mycoplasma-experienced laboratories using quality-controlled ingredients documented to support growth of recent clinical isolates. Without documented proof of adequacy, negative cultures have little meaning.

*M. hominis* grown on solid medium produces colonies of about 200–300 µm diameter, whereas ureaplasma colonies are small (10–70 µm). *M. hominis* may grow on ordinary blood agar where it produces pinpoint colonies after extended incubation. Ureaplasma colonies are too small to be detected on blood agar, but occasionally a scrape from the agar surface will yield ureaplasmas when inoculated into ureaplasma medium. In a few research laboratories only, serological tests have been used to detect antibodies to *M. hominis*, *M. genitalium*, and the ureaplasmas but serodiagnosis cannot be recommended for routine diagnostic purposes.

## Treatment

The genital mycoplasmas have different *in vitro* antimicrobial susceptibilities and resistant strains of all species have been found. Knowledge about the local resistance pattern may often be of value. Furthermore, *in vitro* susceptibility data may not always correlate with clinical experience as exemplified by the apparent *in vitro* susceptibility of most *M. genitalium* strains to tetracyclines in contrast to the lack of eradication in 70–80% of infected patients.<sup>34,35</sup> Before treating *M. hominis* or ureaplasmas, the first consideration is whether to treat or not. The high carriage rate among healthy adults should always be kept in mind.



The main antibiotic classes used for treatment of mycoplasmas are the tetracyclines, the macrolides, quinolones, and clindamycin. Within these classes, significant differences in potency may exist and differences in penetration and accumulation in various tissues should be considered when choosing the antibiotic. Treatment of infections with *M. hominis* can be achieved with tetracyclines, quinolones, and clindamycin, whereas *M. hominis* is intrinsically resistant to macrolides. Ureaplasmas are susceptible to tetracyclines, quinolones, and macrolides, whereas clindamycin is mostly inactive. *In vitro*, clarithromycin is the most potent macrolide, but no large scale clinical trials have been performed to show whether this is a clinically significant difference from other macrolides. In clinical trials, doxycycline appears to be slightly more efficient than clarithromycin in eradicating ureaplasmas, but slightly less clinically efficient and with a higher proportion of gastrointestinal adverse events.<sup>118</sup>

*M. genitalium* is generally susceptible to tetracyclines, macrolides, and quinolones *in vitro*, although tetracyclines are clinically ineffective. Clindamycin is inactive in most strains *in vitro*, but no clinical trials have been performed. Apparently, *M. genitalium* is in most settings highly susceptible to azithromycin.<sup>119</sup> However, recent evidence has suggested that the use of azithromycin 1 g single dose for the treatment of NGU of unknown etiology is strongly associated with high-level macrolide resistance mediated by a single-base mutation in the 23S rRNA gene.<sup>39,120</sup> Thus, the optimal treatment of *M. genitalium* infections may differ according to the local standard therapy for *C. trachomatis* infections and NGU of unknown etiology. Clinical experience suggests that where doxycycline is the drug of choice, azithromycin 500 mg day 1 followed by 250 mg days 2–5 is efficient, whereas in areas where azithromycin 1 g single dose is used for NGU treatment, the extended dosage scheme may fail in 30–90% of the patients. In such treatment failures, moxifloxacin 400 mg od for 7 days appear to be efficient and one of the very few alternatives available.<sup>121</sup>

### Summary

The four mycoplasma species most commonly found in the human urogenital tract are *Mycoplasma genitalium*, *M. hominis*, *Ureaplasma urealyticum*, and *U. parvum*, respectively. Ureaplasmas and *M. hominis* can be found in a large proportion of healthy individuals leading to difficulties in the interpretation of their role as pathogens. *U. urealyticum* appears to be associated with male urethritis when found in large quantities, whereas *U. parvum* has been found more commonly in healthy individuals. *M. hominis* and to a lesser extent the ureaplasmas are strongly associated with bacterial vaginosis making their role in upper genital tract infection in women controversial. In contrast, *M. genitalium* is a well-established cause of non-gonococcal urethritis in both men and women, of cervicitis in women and most likely also of upper genital tract infections in both sexes.

Diagnosis of *M. genitalium* infections rely on nucleic acid amplification tests, as culture is extremely slow and difficult; the preferred treatment is azithromycin in extended dosage as 1 g single dose lead to development of macrolide resistance. Moxifloxacin is currently the only proven alternative in treatment failure after macrolides.

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# Sexually Transmitted Anorectal Infections and Enteric Bacterial Infections

Jason C.B. Goh • S. Joseph Wincelhaus

## 47

### Introduction

The gastrointestinal tract represents an important portal and primary site for sexually transmitted infections (STIs). This chapter describes the anorectal and enteric bacterial conditions separately.

### ANORECTAL SEXUALLY TRANSMITTED INFECTIONS

A significant number of STIs can affect the anorectum. Unless a high degree of awareness is maintained, the protean manifestations of these infections in this anatomical site may be confused with other conditions, resulting in misdiagnosis or delayed diagnosis.<sup>1-3</sup> Accurate diagnosis is important not only because these infections carry a considerable morbidity but also because the associated infections in sexual partners, who may remain asymptomatic, will go undetected.

The perianal skin and the anal canal, which extends for 2 cm up to the dentate line where it meets the rectum, are lined by keratinized stratified columnar epithelium. As such, STIs affecting this area share similar appearances and cutaneous symptoms with those affecting the genitalia, such as herpes simplex virus (HSV), syphilis, chancroid, and genital warts. In addition, the anal canal is richly innervated resulting in intense pain, tenesmus, obstructed defecation, and constipation when affected. Anal intercourse or sex toys may result in anal fissure, rectal prolapse, traumatic rectal bleeding, and retained foreign objects or perforation.

Proximal to the dentate line, the anorectum is a capacious reservoir lined by columnar epithelium.

STIs affecting the rectum can produce inflammation of the rectum known as proctitis, which may cause passage of pus or mucus, rectal bleeding (hematochezia), and sensation of incomplete evacuation (tenesmus). The rectum is innervated via the visceral plexus and is therefore not susceptible to painful cutaneous stimuli like the perianal skin. This explains the relatively asymptomatic nature of rectal STIs and how patients may present to their primary care doctors or even gastroenterologists with symptoms, without making a connection with STIs. If the inflammation affects the distal bowel beyond the first 15 cm

(the length of the rectum), it is often termed distal or left-sided colitis, or proctosigmoiditis. The symptoms of a more extensive distal colitis are those of bloody or mucopurulent discharge and even bloody diarrhea. A pan- or total colitis is the term used to describe total or near total inflammation of the colon.

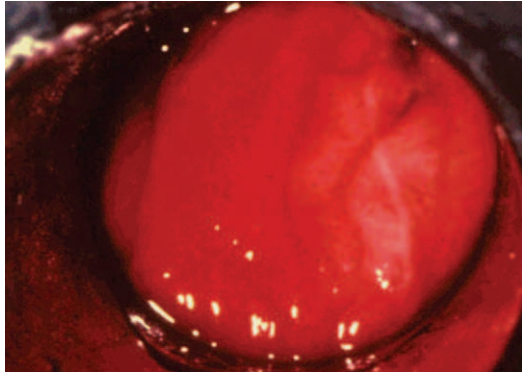
### Inflammatory Conditions

Inflammatory conditions affecting the anorectum, depending on their severity, may or may not be symptomatic. Symptomatic infections commonly present with mucopurulent rectal discharge and/or tenesmus. Three common STIs presenting mainly as inflammatory proctitis are seen in clinical practice: (i) proctitis due to *Neisseria gonorrhoeae*, (ii) proctitis caused by *Chlamydia trachomatis* of the D-K serotypes, and (iii) non-gonococcal and non-chlamydial proctitis.

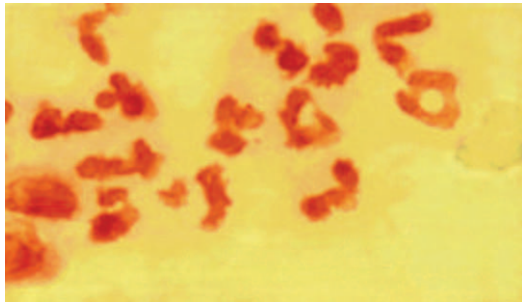
The first two conditions can be seen in men who have sex with men (MSM), women practicing receptive anal intercourse and in women with genital tract infections due to the two agents. The last condition is almost exclusively diagnosed in MSM presenting with sexually acquired proctitis, negative for not only *N. gonorrhoeae* and *C. trachomatis*, but for HSV as well. In the case of women, proctitis due to *N. gonorrhoeae* and *C. trachomatis* may not necessarily be associated with receptive anal intercourse.

### Rectal Gonorrhoea

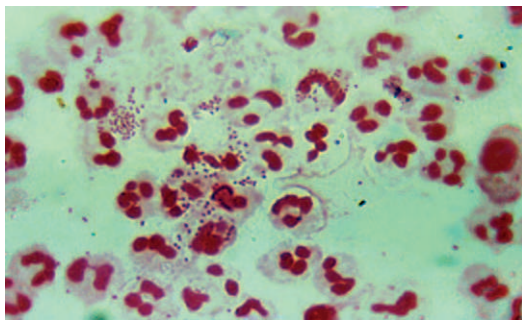
The patient may present with rectal discharge and discomfort 5–7 days after exposure, and on proctoscopy the anal canal and rectal mucosa may appear inflamed and friable (Fig. 47.1). The material for culture and Gram stain should be obtained using a swab inserted through the anus or under direct vision on an anoscope. Gram-stained microscopy of rectal material may reveal a large number of polymorphonuclear leukocytes (Fig. 47.2) and the characteristic gram-negative intracellular diplococci (Fig. 47.3). Cultures should confirm this as *N. gonorrhoeae*. Appropriate antibiotic sensitivity tests on the isolates are nowadays mandatory for the proper management of this infection.



**Fig. 47.1:** In gonococcal proctitis, inflamed and friable rectal mucosa is visible on proctoscopic examination. (Reproduced with permission from: Schofield JB, Wincelhaus SJ. Anorectal manifestations of sexually transmitted infections. *Colorect Dis* 2001;3:74–81).



**Fig. 47.2:** In non-specific proctitis, gram-stained microscopy of rectal material showing a large number of polymorphonuclear leukocytes. (Reproduced with permission from: Schofield JB, Wincelhaus SJ. Anorectal manifestations of sexually transmitted infections. *Colorect Dis* 2001;3:74–81).



**Fig. 47.3:** In gonococcal proctitis, gram-stained microscopy of rectal material showing a large number of polymorphonuclear leukocytes with gram-negative intracellular diplococci. (Reproduced with permission from: Schofield JB, Wincelhaus SJ. Anorectal manifestations of sexually transmitted infections. *Colorect Dis* 2001;3:74–81).

DNA detection techniques that are widely used in the evaluation of urogenital STIs are now being used in anorectal STIs. The ligase chain reaction (LCR) has been shown to be 96.5% concordant with culture and is 99.5% sensitive.<sup>45</sup> However, the use of nucleic

acid amplification tests (NAATs) has not been fully validated in anorectal STIs and is not yet recommended by IUSTI.<sup>6</sup>

It is noteworthy that male sexual contacts of index cases of rectal gonorrhea are more often asymptomatic and serve as the main reservoir for infection.<sup>5,7</sup> Recreational drug use, engagement in anonymous sex, multiple sexual partners, and HIV positivity are also risk factors for rectal gonorrhea and screening for *N. gonorrhoeae* in these at-risk groups who are sexually active is recommended.<sup>8</sup>

Treatment for rectal gonorrhea should follow the standard treatment for uncomplicated urogenital gonorrhea plus concurrent treatment for chlamydia.

### Rectal Chlamydia

Chlamydia genotypes A-K (genotype trachomatis) can be diagnosed by NAAT testing of a rectal swab if facilities are available.<sup>9,10</sup> Otherwise, empirical treatment is recommended with doxycycline 100 mg twice daily orally for 7 days.

### Lymphogranuloma Venereum (LGV)

LGV is an STI due to the LGV serovars of *C. trachomatis* - L1, L2, and L3. It is an infection mainly of the lymphatic system. In the genitoanorectal stage of the infection, which is mostly seen in women and MSM, there is a severe proctitis where the rectal mucosa may appear congested, hyperemic, friable, and studded with multiple superficial ulcers.<sup>7</sup> These changes may extend to the distal colon. The patient may be wrongly treated by gastroenterologists for proctitis of the ulcerative colitis or Crohn disease phenotypes as the relevant sexual history may not be actively sought or volunteered. LGV is described in detail in Chapter 41.

### Non-specific Proctitis

Apart from the specific causes of proctitis mentioned above, MSM practising receptive anal intercourse whose partners develop non-gonococcal and non-chlamydial urethritis very often present with a non-specific proctitis (NSP). Where *C. trachomatis* or *N. gonorrhoeae* cannot be isolated or identified, a diagnosis of NSP is usually made on the findings on microscopy of a gram stained rectal smear showing a large number of polymorphonuclear leukocytes. Occasionally, anorectal HSV infection may present only with inflammatory changes. Traditionally, therefore, infection with this virus is excluded as well before the diagnosis of NSP is established. As in non-specific urethritis, treatment with azithromycin, tetracyclines or erythromycin is often effective.

### Ulcerative Conditions

The common STIs presenting with ulcerative lesions in the anorectum are:

- HSV infection,
- Syphilis,
- Chancroid,
- Donovanosis,
- Cytomegalovirus (CMV) infection,



### Herpes Simplex Virus

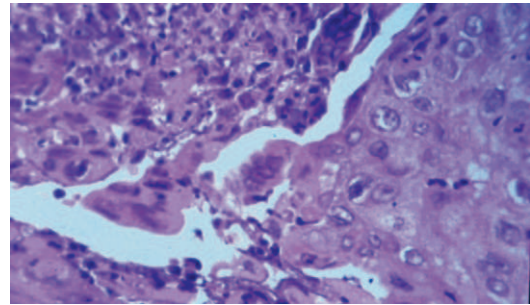
Herpes simplex virus (HSV) infection is the single great masquerader in the anorectal region both in men and women.<sup>1,2</sup> Acute HSV infection can affect the perianal skin, anal canal, and/or the rectum. It can be asymptomatic but usually presents with severe anal pain and may take the form of an ulcerated or friable proctitis or proctocolitis.<sup>11,12</sup> Ulcers may be single or multiple. Solitary ulcers on the anal verge can easily be mistaken for anal fissures. These ulcers may extend on to the perianal skin (Fig. 47.4) and the resulting pain may make clinical assessment difficult. Other associated clinical features to look for include constitutional symptoms of fever and malaise, tender inguinal adenopathy, constipation, and urinary retention.<sup>13</sup> Urinary retention and constipation may occur as painful spasms associated with anorectal HSV and may be a consequence of sacral nerve root involvement.

HSV-2 is responsible for over 90% of anorectal HSV infections and is a common cause of proctitis in MSM practicing receptive anal sex.<sup>14</sup> Yet, HSV-1 may be responsible for a greater or lesser percentage of these infections in various parts of the world depending on the local frequency of oroanal sexual practices. In fact, where there are relatively large gay male populations such as along the eastern seaboard cities of Australia, HSV-1 seems to be responsible for 20–30% of primary anal herpes infections. Condoms seem mostly to be used for penetrative penoanal sex, but dams are hardly ever used for oroanal sex, which may explain this HSV-1 epidemiology.

Following acute infection, the large enveloped DNA virus may remain dormant before reactivating causing asymptomatic infections or relapsing ulcers. Recurrent anal herpes may be seen in up to 40% of patients infected with HSV in the anorectum.<sup>15</sup> However, chronic persistent anal herpes is usually associated with HIV<sup>16</sup> when patients may present with fissures and ulcers



**Fig. 47.4:** Perianal fissures and ulcers of herpes simplex virus infection. (Reproduced with permission from: Schofield JB, Wincelous SJ. Anorectal manifestations of sexually transmitted infections. *Colorect Dis* 2001;3:74–81).



**Fig.47.5:** A histological section of perianal herpes showing spongiotic, ulcerated mucosa, and intranuclear inclusions. (Reproduced with permission from: Schofield JB, Wincelous SJ. Anorectal manifestations of sexually transmitted infections. *Colorect Dis* 2001;3:74–81).

affecting the anal margin and anal canal, sometimes extending into the rectum. Suspecting the diagnosis will give a clue to the underlying immunodeficiency.<sup>2</sup> Relapsing anal herpes may masquerade as recurrent or chronic anal fissures and may confuse an unwary clinician. Crohn disease and solitary rectal ulcer syndrome, especially if the ulcer is surrounded by erythema, may also be confused with anorectal herpes.

Viral cultures and typing from swabs are diagnostic but testing for HSV DNA by PCR is highly sensitive and should be used routinely.<sup>6,15</sup> Ulcer biopsies are taken occasionally, but histopathological features in HSV infection can be quite subtle comprising intranuclear inclusion bodies within epithelial cells at the edge of the ulcer.<sup>17</sup> They show central pallor of the nucleus with peripherally displaced nuclear chromatin (Fig. 47.5).

Although an acute attack is usually self-limiting, treatment with acyclovir or other antivirals as per genital HSV is recommended. Testing for HIV should be offered in all cases.

### Syphilis

Anorectal infection caused by *Treponema pallidum* results in a primary chancre appearing either on the anal verge or in the anal/rectal canal 2–6 weeks following exposure.<sup>18</sup> This is usually seen in MSM infected during receptive anal intercourse.<sup>19</sup> The incidence of syphilis has been rising in recent years and outbreaks have been described in the United Kingdom and elsewhere, primarily among MSM.<sup>20–23</sup> In parts of the USA, the incidence of early syphilis among MSM has doubled between 2003 and 2005.<sup>22</sup>

Ulcers on the anal verge have a firm raised edge and may or may not be painful. Painless lesions could easily be missed or dismissed as traumatic. The primary chancre may not always be associated with inguinal adenopathy in lesions confined entirely to the anorectal area. However, inguinal adenopathy, if present, serves as a useful marker for the infection especially if they are rubbery and painless. Proctoscopic evaluation is necessary to exclude ulcers involving the anal canal or the rectum. Within the anal canal and the distal rectum reported findings include erythema, mucosal ulcers, polyps, and even lobulated masses.<sup>24–26</sup> The associated enlargement of regional lymph nodes with minimal

mucosal non-ulcerative changes can lead to misdiagnosis.<sup>25</sup>

Nevertheless, early anorectal syphilis is far more likely to be diagnosed at the secondary stage than in the primary stage. Patients who reach the secondary stage of infectious syphilis with the ulcers still persisting may also present with fever, maculopapular skin eruptions, and generalized lymphadenopathy. Perianal condylomata lata, the moist and highly infectious soft polypoid growths associated with secondary syphilis, may sometimes be seen (Fig. 47.6). This is usually pruritic and exudative. Within the anorectal canal itself the diverse mucosal lesions described above could still be seen during the secondary stage of the infection.

Where ulcers are accessible, dark field microscopy of serous exudate from the ulcers will show the Treponemes with their characteristic spiral morphology. It has to be interpreted in the context of non-pathogenic spirochetes being an “innocent bystander” within the gastrointestinal tract in some individuals. Histology often reveals a characteristic intense plasma cell infiltrate in early syphilis as seen in chancres and syphilitic gummas. Silver stain and immunofluorescent stain can be useful for detection of the Treponema in the biopsy sample. Where available, multiplex NAAT for *T. pallidum* DNA from the biopsy sample or exudates material can be used.<sup>27</sup>

Direct fluorescent antibody test for *T. pallidum* can be of use where dark field microscopy is not available or in situations where it is not possible to obtain uncontaminated clear serous exudates from the lesions. Serology (VDRL, RPR), syphilis enzyme immunoassay (EIA), and FTA-ABS testing in the very early stages may be negative and may have to be repeated serially. IgG antibody EIA will also be supportive. These sensitive tests could



**Fig. 47.6:** Moist, polypoid lesions of perianal condylomata lata. (Reproduced with permission from: Schofield JB, Wineslaus SJ. Anorectal manifestations of sexually transmitted infections. *Colorect Dis* 2001;3:74–81).

be particularly valuable in the serological diagnosis of anorectal syphilis in HIV-infected persons. The IUSTI recommend HIV testing in all patients with syphilis.<sup>6</sup> See Chapter 36 for treatment.

### Intestinal Spirochetosis

While intestinal spirochetes are a causative agent of diarrhea in animals, their role in the human gut is not at all well-defined. While this does not cause anorectal ulcers, it is described here alongside rectal syphilis. Although a syndrome of diarrhea and rectal bleeding has been ascribed to intestinal spirochetes of the genus *Brachyspira* in a part of Italy,<sup>28</sup> many other studies do not support a causal relationship.<sup>29–31</sup> Intestinal spirochetes have been diagnosed in 36–39% of asymptomatic MSM but its prevalence in heterosexual men has not been specifically studied.<sup>32,33</sup>

Intestinal spirochetes are readily identified on hematoxylin and eosin stain.<sup>30,31</sup> Current opinion is that intestinal spirochetes do not cause disease and they are an incidental finding even in patients with symptoms. In exceptional cases where other causes of diarrhea have been excluded or unsuccessfully treated, oral Metronidazole 400 mg three times a day for 10 days may eliminate the spirochetes and relieve symptoms. Treatment for asymptomatic intestinal spirochetosis cannot be recommended.

### Chancroid

Chancroid is caused by the gram-negative bacillus *Haemophilus ducreyi* and is a common cause of genital ulcer in the developing countries of Africa, Asia, and South America, with the highest prevalence reported from southern, central, and eastern Africa.<sup>34</sup> Its link with heterosexual HIV transmission is well-established.<sup>35,36</sup>

Anal infection occurs mostly in women and MSM, and the resulting non-indurated, often-painful ulcers can be destructive. Although the infection can sometimes be asymptomatic in women, tenesmus and rectal bleeding may be the presenting symptoms. Initially, the ulcers tend to be discrete with irregular, undermined edges and greyish yellow base. The ulcers soon coalesce destroying the soft tissues in and around the anus. The suppurating inguinal lymphadenopathy seen with genital lesions may not be seen if the primary infection affects only the anal canal. The differential diagnosis of such anorectal ulcers remains HSV and syphilis depending on the sociogeographical context. *H. ducreyi* infection of the rectum has not been well-documented probably because of the lack of awareness amongst clinicians and the paucity of reliable diagnostic tests available for the condition.

Available diagnostic tests vary depending on the setting in which the infection is suspected. Direct Gram-stained microscopy from scrapings of the ulcers showing the typical “schools of fish” appearance of the gram-negative bacilli is no longer accepted as a reliable method of diagnosis. Different selective enriched culture media are now available for growing the fastidious *H. ducreyi* as well as sensitive PCR assays. This is described further in Chapter 36.



### Donovanosis

Donovanosis or granuloma inguinale is caused by the gram-negative bacillus *Klebsiella granulomatis*. Endemic foci are found in Papua New Guinea, Southeast India, South Africa, Zimbabwe, West Indies, Brazil, northern and central Australia, Vietnam, and Japan. A male preponderance has been noted in most reported series.<sup>37</sup> Although genital and inguinal regions are the common sites of infection, primary perianal infections have been reported.<sup>38,39</sup> After a variable incubation period, the primary site of infection is marked by a papule or nodule, which soon breaks down to the typical red, raw, painless ulcer. The condition is marked by great chronicity and is accompanied by feelings of shame due to the highly offensive smell associated with the larger lesions.<sup>37,40</sup> Late presentation with advanced disease is extremely common due to the stigma associated with this disease in the affected communities.

Primary perianal infection, mostly seen in MSM (Fig. 47.7), may extend to the anal canal and cause rectal bleeding. Chronic lesions may lead to rectovaginal fistulae, or fistulae connecting the rectum to other pelvic organs. Distinguishing chronic lesions in the rectum from malignancies or fistulizing Crohn disease of the perineum may be clinically very difficult.<sup>37</sup> The ulcers spread by soft tissue destruction and the accompanying sclerosis can result in stenosis of the anal canal.

Examination of tissue specimens from the ulcer remains the mainstay of diagnosis of donovanosis. Various staining techniques have been reported to stain cellular material for the presence of Donovan bodies.<sup>37,41</sup> These include, Giemsa or modified Giemsa stain, Leishman stain, and Wright stain. Silver impregnated stains such as Warthin–Starry stain can also be used to stain biopsy tissue. The Donovan bodies are seen as bipolar dense encapsulated organisms stuffed within macrophages. Although culture, PCR



**Fig.47.7:** Red, raw, granulomatous ulcers of donovanosis in perianal region. (Reproduced with permission from: Schofield JB, Wineslaus SJ. Anorectal manifestations of sexually transmitted infections. *Colorect Dis* 2001;3:74–81).

methods, and serological tests for the diagnosis of donovanosis have been described; these have not come into general use yet. For treatment refer to Chapter 43.

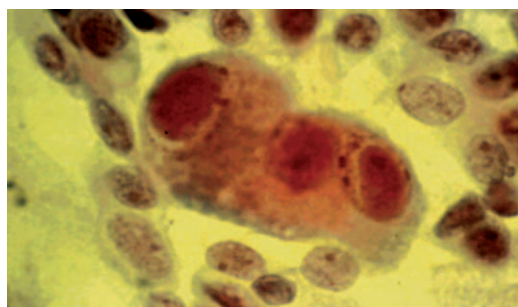
### Cytomegalovirus Infection

Symptomatic cytomegalovirus (CMV) infection of the rectum or colon is often seen in the context of existing inflammatory bowel disease or immunosuppressed individuals, particularly post-transplantation patients taking antirejection therapy, but is also being increasingly seen in apparently immunocompetent individuals.<sup>42,43</sup> It can also be sexually transmitted in both immunocompetent and immunocompromised hosts. In patients with advanced AIDS, typically those with CD4<sup>+</sup> count of less than 100/ $\mu$ L<sup>3</sup>, CMV can be a causative agent of ulcerative esophagitis, gastritis, proctitis, and proctocolitis.<sup>44,45</sup> Infection is more often due to reactivation of a latent infection but can be primarily acquired.

CMV esophagitis may coexist with candidiasis and present with odynophagia and heartburn. Diarrhea may be watery or bloody depending on the degree of ulceration and extent of colonic involvement. CMV colitis is often associated with a systemic syndrome of fever, loss of appetite, malaise, abdominal pain, and diarrhea. The fulminant form of colitis may lead to toxic dilatation and even perforation.<sup>42,46</sup>

Sigmoidoscopic appearance is similar to that of a confluent colitis but ulceration may be more prominent. Stool cultures are negative for conventional viral and bacterial pathogens. Taking random biopsies are essential for diagnosis. The pathologist needs to be alerted to look out for features of CMV including giant cells with basophilic intranuclear and intracytoplasmic viral inclusion bodies (Fig. 47.8). Specific immunostaining for CMV can be performed on the biopsy samples, and viral cultures and PCR can be performed where available.

In patients with systemic illness, blood and urine may test positive for CMV PCR. Most patients with CMV colitis tend to secrete CMV in the urine. Estimating IgG antibodies against CMV in the serum may not be helpful because of the wide prevalence of the latent infection in the at-risk population. IgM response to reactivation of the disease may not be forthcoming



**Fig.47.8:** Giant cell of CMV infection in a histological section. (Reproduced with permission from: Schofield JB, Wineslaus SJ. Anorectal manifestations of sexually transmitted infections. *Colorect Dis* 2001;3:74–81).



in the immunocompromised patient. Measurement of CMV viral load in the serum may be helpful, as the viral load tends to be high during active infection or reactivation.<sup>42,47,48</sup> In patients with confirmed CMV colitis, HIV testing should be considered.

Treatment with Ganciclovir is often effective, with foscarnet and cidofovir as second-line back-up. Relapses can occur and may require some form of maintenance prophylactic therapy until immune function can be restored. The fulminant form resulting in toxic dilatation and intestinal perforation may require colectomy as with patients with inflammatory bowel disease.

### Idiopathic Ulceration in HIV Infection

As in any part of the gastrointestinal tract, anorectal ulceration without apparent cause is common in HIV infected individuals. They can be extremely painful and occasionally cause destruction of the anal sphincter complex. It has been suggested that the HIV infection itself may be directly responsible for these so called “idiopathic” ulcers.<sup>49</sup> However, this diagnosis can only be made after excluding all other causes of anorectal ulcerations in this patient group. Treatment options include topical (intralesional steroid), systemic (thalidomide, prednisolone), and surgical (excision biopsy).<sup>50</sup> They may also resolve with HAART.

## Tumors

### Human Papillomavirus Infection

STIs due to the genital types of human papillomavirus (HPV) infection are becoming increasingly common. The infection may involve the anus and the anal canal but never above the dentate line. These cauliflower-like lesions should be distinguished from squamous cell cancer of the anus and condylomata lata of secondary syphilis.

While it usually affects MSM practicing receptive anal intercourse (Fig. 47.9),<sup>51</sup> it can also be seen in some heterosexual men and women who have never had anal sex.<sup>52</sup> HPV types 6 and 11, which are not linked to anal cancer, cause the majority of anal warts. On the other hand, infection with the oncogenic HPV types 16, 18, 31, 35, 45, and other “high-risk” serotypes, if persistent can lead to anal intraepithelial neoplasia and progress to squamous cell carcinoma of the anus and the anal canal.<sup>53</sup>

Alarming, a community-based study in Sydney using a combination of Digene Hybrid Capture 2 and the Roche linear array assays found almost universal anal HPV infection in the MSM community they sampled.<sup>54</sup> HIV positive men are more likely to be infected with diverse and multiple HPV genotypes than HIV negative men.<sup>54</sup> HPV infection presenting as warts is the most common perianal condition in HIV infected patients in whom the warts tend to be more exophytic and numerous compared to their immunocompetent counterparts.<sup>55</sup> This may in part be due to the reduced immune surveillance but may also be due to infection with multiple and high-risk serotypes.<sup>54–57</sup>

Dysplasia has been reported in 10% of anal warts seen in HIV infected patients.<sup>58</sup> As this is not always associated with obvious warty change seen by naked eye examination, cytological



**Fig. 47.9:** Perianal human papillomavirus infection. (Reproduced with permission from: Schofield JB, Wincelhaus SJ. Anorectal manifestations of sexually transmitted infections. *Colorect Dis* 2001;3:74–81).

screening or biopsy may be necessary for confirmation. Although squamous cell carcinoma of the anorectum triggered by HPV may affect non-HIV infected patients, an increased surveillance is important in the presence of HIV/HPV co-infection although the best screening modality and its efficacy remain unclear.<sup>59</sup> HAART therapy may not reduce the risk of progression to anal intraepithelial neoplasia. Currently available HPV vaccines can potentially prevent the majority of squamous cell carcinoma of the anus but clearly they have to be given before the onset of sexual activity.<sup>60</sup>

The wide variety of treatment for HPV reflects their relative lack of efficacy. Anal HPV can be treated with topical podophyllin but this can potentially result in anal stenosis with long-term use. Cryotherapy is effective but large anal warts in HIV positive individuals may be recalcitrant to treatment. Laser therapy and even surgical excision may be used in these refractory cases. Other treatments such as polyphenon, imidazoquinoline derivatives, and more novel techniques such as Argon plasma photocoagulation and ultrasound-driven Harmonic scalpel have all been advocated with variable outcome. A recent study from London revealed a 63% cure rate, defined as 12-month disease-free state for anal intraepithelial neoplasia using laser ablative treatment.<sup>61</sup>

### Kaposi Sarcoma

Tumors associated with HIV that can be found in the anorectum or elsewhere in the gastrointestinal tract include Kaposi sarcoma (KS) and lymphoma.<sup>62</sup> After the skin, the GI tract is the most common site for KS. AIDS-associated KS affects MSM more commonly than the other groups. There is compelling evidence that the human herpes virus-8 (HHV-8), the etiological agent of KS, may also be sexually transmitted—at least in MSM.<sup>63–65</sup>

In the anorectum, the condition may manifest as a nodule or merely as a discolored patch or plaque. The development of KS in patients with HIV and HHV-8 co-infection may correlate with the degree of immunosuppression seen in these patients. The further advanced the immunosuppression, the more likely it is for HHV-8 to reactivate resulting in KS. This is further borne out by the fact that KS-associated lesions generally regress with the initiation of highly active antiretroviral treatment against HIV.<sup>66</sup> Biopsy and histological examination of suspected lesions remain the commonest method of diagnosing KS. In typical cases, the “sarcoma” is represented by vascular channels with extravasated red blood cells surrounded by spindle-shaped tumor cells. Early lesions, however, may be difficult to diagnose histologically and may not show anything more than a “granulation tissue-like” appearance.<sup>62</sup>

### SEXUALLY TRANSMITTED ENTERIC BACTERIAL PATHOGENS

The principal bacterial pathogens that can be sexually transmitted and cause enteritis (profuse watery diarrhea) and/or colitis include *Shigella*, *Salmonella*, and *Campylobacter*. They are more prevalent in MSM and patients with AIDS than other groups.

Diarrhea is a common symptom in HIV infection. It can be a significant presenting symptom of HIV infection especially in the developing world. The prevalence of persistent and chronic diarrhea has been estimated to be between 17% and 95% for developed and the developing worlds, respectively.<sup>67</sup> Causes of diarrhea include primary HIV infection itself, HAART (especially the protease inhibitors), lymphoma, common pathogens causing gastroenteritis (viral, *Campylobacter*, *Salmonella*, and *Shigella*), and opportunistic infections (viral, bacterial, protozoal, and fungal).

The specific bacterial enteric pathogens that are sexually transmitted are considered below.

### Shigella

*Shigella* comprises a group of gram-negative enteric bacteria that includes four major subgroups—*S. dysenteriae* (group A), *S. flexneri* (group B), *S. boydii* (group C), and *S. sonnei* (group D). *S. dysenteriae*, also known as the shiga bacillus, produces the most severe form of dysentery; while *S. sonnei* produces the mildest disease. In tropical countries, the most common organism is *S. flexneri*, while in United States, most of the bacillary dysentery is caused by *S. sonnei*.

Humans serve as the only reservoir and natural host for *Shigella*. As few as 10 *Shigella* organisms can cause overt clinical illness in volunteers. Most of the transmission is person-to-person and is facilitated by close human contact. The low inoculum of *Shigella* required for transmission and the ability of *Shigella* to survive in acidic conditions during transit through the stomach leads to easy spread of *Shigella* where crowding, poor sanitation, and poor personal hygiene co-exist.

Outbreaks of Shigellosis have been described among communities of MSM in the developed world.<sup>68–70</sup> A case-control study in San Francisco, US, identified risk factors for Shigellosis among men: MSM (Odd ratio 8.24), HIV (OR 8.17), direct oral-anal contact (OR 7.5), and foreign travel (OR 20).<sup>71</sup> This contrasted with women in whom the only identifiable risk factor was foreign travel (OR 21). In a questionnaire study from Berlin, most men had direct or indirect oral-anal sexual contact in the week before they fell ill with Shigellosis.<sup>70</sup>

The pathogenesis of *Shigella* infection depends primarily on a large plasmid that encodes factors permitting the bacteria to enter cells, grow freely in the cytoplasm, and spread directly to adjacent cells.<sup>72</sup>

*Shigella* is able to invade both the colonic enterocytes (epithelial cells) and the specialized M cells that overlie lymphoid follicles. *Shigella* invades epithelial cells from the basolateral surface by use of a type III secretion apparatus, which confers its virulence factor. Two proteins secreted via the type III apparatus, Ipa A and Ipa C, are inserted into host cell membranes and appear to mediate cell entry directly.<sup>73,74</sup> The bacteria then spread to adjacent cells and to macrophages which they kill by inducing apoptosis while releasing IL-1.<sup>75</sup> Although enterotoxins are expressed, their contribution to the disease process is unclear.

Clinically, *Shigella* dysentery is characterized by high fever, toxemia, abdominal cramps, tenesmus, frequent bloody mucoid stools, and vomiting. The spectrum of *Shigella* includes asymptomatic infection to severe dysentery.

The incubation period is 1–4 days. The progression of disease occurs through distinct phases in shigellosis. At the onset of clinical illness, there is toxemia and high fever, followed hours later by watery diarrhea. Later, it leads to passage of scanty stools of blood and mucus. Severe dysentery is most likely to occur in infection with *S. dysenteriae* type I, less commonly with *S. flexneri*, and is least likely in *S. sonnei* infection. Colonoscopy shows hemorrhagic mucosa with mucus discharge, and focal ulcerations and sometimes an exudate. With extensive colonic involvement, protein-losing enteropathy, toxic megacolon and even perforation can occur. Hemolytic uremic syndrome, leukemoid reactions, and severe hypoproteinemia are recognized complications of *Shigella* dysentery. Rarely, Reiter syndrome follows shigellosis, particularly that due to *S. flexneri* serotypes.

Culture of a fresh stool is optimal. Stool microscopy often shows a great abundance of neutrophilic fecal leukocytes. Measurement of serum antibodies to the O antigen of the specific *Shigella* serotype by ELISA is useful in investigation of outbreaks.

In general, antimicrobial therapy is not indicated for the treatment of *Shigella*, except in those with bloody diarrhea, AIDS or sickle cell disease.<sup>6</sup> However, antibiotic treatment in cases of symptomatic positive stool cultures has been advocated for public health reasons.

It has been shown that appropriate antibiotics significantly decrease the duration of fever, diarrheal illness, and excretion of the pathogen.<sup>76</sup> Resistance to sulfonamides, streptomycin, chloramphenicol, and tetracycline is almost universal and many

*Shigella* are now resistant to ampicillin and trimethoprim-sulfamethoxazole. Where indicated, the drug of choice is ciprofloxacin or nalidixic acid. No antibiotic treatment is recommended for the convalescent carrier stage. Patients with AIDS who develop chronic carriage may require prolonged treatment with a quinolone. Rifaximin is currently being evaluated as prophylactic medication for travelers to hyperendemic regions. For food handlers with Shigellosis, three consecutive negative stool samples taken not less than 24 hours apart, and at least 2 days after cessation of antibiotic therapy should be obtained before they are allowed to return to work.<sup>6</sup>

## Salmonella

There are more than 2000 serotypes of *Salmonella*. Of these, the non-typhoidal *Salmonella* are important causes of infective gastroenteritis and are discussed below in the context of potential oral-fecal sexual transmission and their significance in patients with AIDS. Typhoid fever is an acute systemic illness caused by infection with *Salmonella typhi*. Sexual transmission is uncommon but has been reported anecdotally.<sup>77</sup> Typhoid fever is not discussed here.

### Non-typhoidal Salmonellosis

Common serotypes of non-typhoidal *Salmonella* include *S. typhimurium*, *S. heidelberg*, *S. enteritidis*, *S. newport*, and *S. badar*. Poultry has the highest incidence of *Salmonella* carriage, particularly hens, chickens, and ducks.

Clinical syndromes seen with *Salmonella* are: (i) gastroenteritis, (ii) bacteremia, (iii) localized infection of bones, joints, gallbladder, and meninges. The most common syndrome is gastroenteritis. The usual incubation period is 6–48 hours. Initially, nausea and vomiting are followed by abdominal cramps and diarrhea. The diarrhea is accompanied by fever and bloody stools in 50% of the cases. Occasionally, the patient may develop toxic megacolon and perforation. The course of disease ranges from 1 to 3 weeks.

Sexual transmission of *Salmonella* is uncommon and anecdotal. There is an estimated 20-fold increase in incidence of *Salmonella* infection in patients with AIDS.<sup>78</sup> Patients are more likely to suffer from a more severe clinical illness, bacteremia, and are more likely to have relapses.<sup>79,80</sup> *S. typhimurium* and *S. enteritidis* are responsible for most cases in these patients, and *Salmonella* bacteremia is an AIDS-defining illness. Dysregulation of the proinflammatory cytokine response, including IL-12, by macrophages during *Salmonella* infection in patients with HIV has been implicated as a mechanism for severe clinical disease and bacterial persistence in these patients.<sup>79,81</sup>

Stool culture often yields the diagnosis. Antimicrobial therapy is not advocated for most cases of *Salmonella* gastroenteritis. Treatment does not alter the rate of clinical recovery and antibiotic therapy has been thought to increase the incidence and duration of intestinal carriage of these organisms. Nevertheless, antibiotic treatment is advisable in certain clinical scenarios including severe *Salmonella* colitis or *Salmonella* gastroenteritis in patients with

AIDS, lymphoproliferative disease or sickle cell disease. In acute bacteremia in patients with AIDS, a 2-week course of ciprofloxacin 750 mg twice a day is first-line treatment although this may need to be modified according to the bacterial antibiotic sensitivity pattern. Recurrence of *Salmonella* bacteremia can be as high as 45% in patients with AIDS. Long-term suppressive treatment with ciprofloxacin 500 mg twice a day may be necessary.

## Campylobacter

*Campylobacter jejuni* is one of the most common causes of acute infective gastroenteritis in the world.

Transmission occurs following ingestion of incompletely cooked chicken or other meats and non-pasteurized milk. Person-to-person transmission can also occur in close household contacts and preschool children. Sexual transmission is via the oral-fecal route especially among MSM.<sup>82–85</sup> In a study performed in Baltimore, *Campylobacter* species were isolated from 4%, 20%, and 9% of MSM who were asymptomatic, who had symptomatic diarrhea and who had AIDS, respectively.<sup>86</sup>

*Campylobacter* enteritis produces a syndrome of fever, diarrhea, and abdominal pain. The disease is usually self-limiting and lasts for 1–7 days. Severe bloody diarrhea may mimic acute inflammatory bowel disease and may even be complicated by a fulminant colitis, pseudomembranous colitis, toxic megacolon, and pancreatitis. It is a known cause of post-infective Guillain-Barre syndrome, reactive arthritis, and myopericarditis.

Diagnosis is often obtained by positive stool cultures.

Use of antibiotics is controversial. In patients with bloody diarrhea, fever or worsening symptoms, treatment with erythromycin (500 mg four times a day for 7 days), azithromycin (500 mg daily for 3 days), or ciprofloxacin (250 mg twice daily for 7 days) is recommended. Strains of ciprofloxacin-resistant *Campylobacter* have however emerged worldwide.<sup>86,87</sup>

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# section **viii**

## **FUNGI, PROTOZOA, AND ARTHROPODS** — *Charlotte A. Gaydos*

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## Vulvovaginal Candidiasis

### INTRODUCTION

Vulvovaginal candidiasis (VVC) is the most common cause of vaginitis in the tropics and second only to bacterial vaginosis (BV) in the developed nations. About 70–75% of women will have at least one lifetime episode, with 40–50% suffering a recurrence.<sup>1</sup> In 20%, *Candida* may colonize the vagina without producing any symptoms.<sup>2</sup> Overall, 85–90% of candidal vaginitis is caused by *Candida albicans*.<sup>3</sup> Other species in order of incidence include *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei*, and *Candida guilliermondii*.<sup>4</sup>

VVC includes primary infection, which may be sporadic and is often considered idiopathic, although there is some evidence that sexual intercourse may be a precipitating factor in many cases. VVC may be secondary to other predisposing causes, such as pregnancy, antibiotic usage, diabetes mellitus, and estrogen therapy.

Recurrent vulvovaginal candidiasis (RVVC) occurs in about 5% women.<sup>3</sup> This may be associated with immunosuppression, diabetes mellitus, and may be caused by non-*C. albicans* species. The latter patients may require more complex investigations including full identification and sensitivities.

VVC and RVVC are increasing in incidence and cost. A study in the US showed that in 1995, these conditions cost US \$1.8 billion and it is predicted that by the year 2014, this will rise to US \$3.1 billion. This study also estimated that wrong self-diagnosis may occur in up to 50% of women.<sup>5</sup> There is a concern about the use of over-the-counter and alternative medicines, which may hide or delay the diagnosis of other more serious underlying conditions.<sup>6</sup> There have been interesting developments in the understanding and management of mucocutaneous candidiasis,<sup>7</sup> and also its association with thymoma<sup>8</sup> and the autoimmune polyendocrine syndromes.<sup>9</sup> However, many of these developments are out of the scope of this chapter.

Centers for Disease Control and Prevention (CDC) classification of VVC is shown in Table 48.1.<sup>10</sup>

**Table 48.1:** Classification of Vulvovaginal Candidiasis (VVC)<sup>10</sup>

Uncomplicated
<ul style="list-style-type: none"> <li>• Sporadic or infrequent VVC</li> <li>• Mild-to-moderate VVC</li> <li>• Likely to be <i>C. albicans</i></li> <li>• Non-immunocompromised women</li> </ul>
Complicated
<ul style="list-style-type: none"> <li>• Recurrent VVC</li> <li>• Severe VVC</li> <li>• Non-<i>C. albicans</i> candidiasis</li> <li>• VVC in women with uncontrolled diabetes, debilitation, or immunosuppression, or those who are pregnant</li> </ul>

### HISTORY

Vaginal candidiasis was first described in 1849 and the pathogen was named *Oidium albicans* in 1853.<sup>11</sup> The name was derived from the word *Candida* describing the white robe (toga) worn by Roman Senators and this name was adopted internationally in 1954.<sup>12</sup> Candidal balanitis was first reported in 1920.<sup>13</sup> Over the years with the increasing use of invasive procedures and broad-spectrum antibiotics in medical management, systemic candidiasis has become a major problem in hospitals. It has become important in immunosuppressed patients such as those infected by human immunodeficiency virus (HIV)<sup>14</sup> and in those suffering from neutropenia, e.g., post-bone marrow or solid organ transplantation. Genitourinary Medicine Clinics in the UK have shown an increase in genital candidiasis from 118/100,000 patients in 1975 to 200/100,000 in 1984.<sup>15</sup> In the Western world, it may also be related to the use of tight clothing (including G strings),<sup>16</sup> the increased use of colored and perfumed agents in the genital region, and procedures such as shaving and waxing.

### EPIDEMIOLOGY

*Candida* species are found in humans, animals, and many foodstuffs particularly fruit juices (probably packaging contamination). In humans, *Candida* species are found in the oropharynx and the



rest of the gastrointestinal tract and from there they colonize to the vulvovaginal area. As VVC and RVVC are not reported as sexually transmitted infections, there are limited epidemiological data. Many patients self-treat and present to practitioners only when there is no response to usual household remedies.

VVC is not common in premenstrual girls. It peaks in incidence at 20–40 years of age, and is found in postmenopausal women who are on estrogen supplements or may have underlying pathology.

About 20% of asymptomatic healthy women of childbearing age group carry the infection but this can range between 10% and 50%. About 50% of college women by the age of 25 will have had at least one physician-diagnosed episode of VVC.<sup>1</sup> There has been little research into behavioral factors associated with VVC. However, there is confirmed transmission by vaginal sexual intercourse and other forms of sexual activity including orogenital contact. Eight hundred women attending two sexual health clinics in London for lesbian and bisexual women completed a questionnaire and 88% had a full sexual health check. VVC was associated with more sexual partners and the authors suggest that *Candida* could be sexually transmitted among women.<sup>17</sup> VVC is more common in pregnancy with about 10% of the women in the first trimester and 36–50% in the third trimester having symptomatic disease. Overall, symptomatic disease occurs in 60–90% of pregnant women.<sup>18</sup> A recent study by Foxman et al.,<sup>19</sup> which included interviewing 2000 women, determined that the incidence of RVVC in the US is approximately 8% in women of reproductive age.

There has been an improved understanding of the epidemiology of candidal infections because of developments in typing methods involving serological techniques (serotypes A and B), DNA typing, and southern blot hybridization.<sup>20</sup> Serotype B is more commonly found in immunocompromised patients. It is the predominant type in Europe. Whereas, in the US, both types A and B are common, and in Hong Kong, serotype A strains predominated in blood culture isolates. The majority of the typing surveys have been done in patients with disseminated disease, including heroin addicts, who may have specific biotypes. Typing methods have confirmed that most of the recurrences in RVVC are caused by the same strain; the yeast may reside in protected rectal sites. *C. albicans* generally does not become resistant to antimycotics even after intermittent and prolonged courses of antifungal agents.<sup>21,22</sup>

In one study, 18 patients with RVVC were assessed with DNA probes and it was found that in sequential episodes, the strains were identical, sustaining the maintenance of the same strain. The isolates from oropharynx and vulvovaginal areas were also same or closely related in 80% of the patients. The isolates were the same in the male partners of 8 patients. These findings support the hypothesis that RVVC is due to vaginal relapse of a persistent yeast infection.<sup>23</sup>

In another study, a DNA probe was used to strain-type isolates from vagina and rectum in 121 women including 22 women with RVVC. Of the 78 women, who were culture positive,

22 women became culture negative after local application of clotrimazole, but again became culture positive within 12 weeks. Another 12 women remained culture positive at follow-up (persistent carriage). Women with asymptomatic persistent infection had significantly lower viable candidal counts at their post-treatment follow-up visit. Of the 66 women with positive cultures for *C. albicans* in both vagina and rectum, 52 had genetically identical isolates. This study also found that there was no evidence of resistance to either fluconazole or clotrimazole in immunocompetent persons with recurrent infection or persistent carriage of *Candida*.<sup>24</sup>

## MYCOLOGY

The most common human mycoses are caused by the genus, *Candida* and often cause opportunistic infections as these yeasts can exist as common commensals that colonize epithelial surfaces. *Candida*, classified as yeast, is a dimorphic fungus that forms budding blastoconidia, which elongate into pseudohyphae and these can develop into true hyphae. *Candida* is in the class of Blastomycetes but under the order Cryptococcales. More than 200 species have been classified, but there are less than 10 non-*C. albicans* species that are frequently associated with infections. These species can be identified by their colony characteristics, microscopy, biochemical reactions such as fermentation, assimilation of sugars, and growth in different nutrient media.<sup>25</sup> In a recent study, non-*C. albicans* species were isolated in 11% of women with vulvovaginal yeast carriage who reported to primary care hospitals. Various non-*C. albicans* species isolated were *C. glabrata* (69%), *C. parapsilosis* (9%), *C. krusei* (9%), *C. tropicalis* (6%), *C. cerevisiae* (5%), *C. kefyr* (1%), and *C. humicolus* (1%).<sup>26</sup> *C. albicans* grows on Sabouraud agar as shiny, cream-colored, yeasty-smelling, smooth-surfaced colonies. On wet-preparation microscopy, spherical budding yeast cells with pseudomycelium are seen. The germ tube test where the yeast produces hyphal germ tubes when incubated at 37°C in serum for 2 or 3 hours, is the classic diagnostic test. Chlamydospore formation on cornmeal polysorbate 80 agar at 22°C to 25°C in 48–72 hours confirms the identity.<sup>27</sup> The two genera *Candida* and *Torulopsis* have now merged and *C. glabrata* is the most common cause of non-*C. albicans* infections. *Saccharomyces cerevisiae* (bakers and brewers yeast) also causes clinical VVC. Non-*C. albicans* yeasts are often variable in their sensitivity to antimycotic agents and sensitivity tests are required, if there is complicated or recurrent disease. *Candida* transmission probably occurs through its yeast form that is present in asymptomatic infection. The pseudomycelial form is associated with invasion and symptomatic infection. The phenomenon of phenotypic switching is visible as different colony types appear white and opaque on culture. These have differences in their hyphal-forming capacity, generation time, and sensitivity to low and high temperatures. The yeast develops into a hypha with the expression of virulence genes that can encode hyphal wall protein; cyclic AMP plays a role through *C. albicans* cyclase-associated protein gene.<sup>28</sup> Switching may also enhance adhesion

and the secretion of pathogenic enzymes such as phospholipases, aspartate transaminases, and other proteinases.<sup>29</sup>

## **PATHOLOGY**

*Candida* most commonly causes superficial infection. It can also cause locally invasive disease or systemic infection. Superficial candidiasis is associated with swelling (edema), redness, and sometimes, superficial ulceration. Immunosuppressed patients may have locally invasive candidiasis, e.g., esophagitis, which may manifest as mucosal ulcerations with or without a pseudomembrane.

Microscopically, an acute inflammatory reaction occurs, which can be seen on hematoxylin and eosin, periodic acid-Schiff (PAS), and silver stain. These stains reveal oval yeasts as well as pseudohyphae, which along with necrotic debris, make up the typical vaginal wall white plaques of candidal infection. In ulcerated lesions with more localized invasion, there may be a pseudomembrane on top of the ulcer, excess of fibrin, pseudohyphae, and necrotic debris.<sup>30</sup>

## **PATHOGENESIS**

### **Microbial Pathogenesis**

#### **Adherence**

*C. albicans* has the greatest affinity for adhering to vaginal epithelial cells, followed by *Candida tropicalis* and *Candida parapsilosis*. Adherence is dependent on many factors including the local environmental milieu. These factors include the presence of other microorganisms that may be competing for cellular binding sites; nutrients such as glucose, the concentration of hormones, particularly estrogen, which increases the avidity of epithelial cells for *C. albicans*, and the presence of immunoglobulin A (IgA), which may interfere with adherence.<sup>31</sup>

Cell surface hydrophobicity of *C. albicans* is important in adherence. Germ tube formation is associated with a significant rise in cell surface hydrophobicity.<sup>32</sup> Initial adherence is dependent on unidentified receptors, adhesions related to fibronectin. The mannoprotein component on the yeast surface probably plays a role and is associated with impaired phagocytosis. Adherence leads to colonization and increased population density is associated with symptomatic/invasive disease.

#### **Invasion**

Germ tube hyphae have a different surface immunogenicity that could fool immune mechanisms and at the same time, potentiate invasion by production of multiple enzymes, mostly proteinases.<sup>22</sup> Proteinases break down peptide bonds, phospholipases enhance invasion, carboxyl phospholipases are proteolytic to keratinocytes, and aspartate proteinases are collagenolytic. These along with hyphae can actually lead to invasion through cells. Secreted aspartate transaminases are encoded by 10 different genes. The genes, which are important for infections of skin and mucous membranes, are

different from those important in systemic infections.<sup>33</sup> These enzymes may also break down local immunoglobulins.<sup>34</sup>

Fidel's group has studied the pathogenesis of candidiasis for decades often in experimental animals. A study using women as a live challenge model showed that asymptomatic women had a non-inflammatory response. Symptomatic women had an aggressive immune response with neutrophil infiltrates.<sup>35</sup>

Another group of researchers studied the levels of hyaluronan, an anti-inflammatory immune system activator released into vaginal secretions. *C. albicans* strains can produce hyaluronidase. Hyaluronan levels in a small group of women were shown to be increased in RVVC infections not on treatment, compared to controls and those on fluconazole. High levels were also associated with itching/burning or itching/discharge symptoms. The authors inferred that there may be 2 subsets of RVVC that may have implications for therapy.<sup>36</sup>

## **HOST-DEFENSE MECHANISMS**

### **Natural Barriers and Precipitating Factors**

The integrity of a mucosa with the stability of local factors is an important defense against invasion. Factors like pH (as germ tube formation is maximal at pH 6), the presence of glycogen (which is increased by estrogens, natural, cyclical, or iatrogenic), increased glucose levels (as in diabetes and high sugar intake), and high iron levels facilitate virulence. Other factors like physical trauma, increased moisture, occlusion (nappies, sanitary towels),<sup>37</sup> loss of normal microbial flora (post antibiotics or replacement with other organisms), and the use of steroids (that interferes with polymorph phagocytosis) may jeopardize the normal environment<sup>31,34</sup> allowing opportunism.

### **Humoral Immunity**

Although patients with IgA deficiency are not known to be particularly susceptible to candidal infections, humoral immunity does have some part to play in the initial local defenses. High levels of IgA can be found in infected patients, but they do not prevent colonization; therefore, there is no role for the use of gammaglobulins as treatment of RVVC.

In RVVC, 25–33% of women may be genetically predisposed. The non-secretors of Lewis blood group have greater than 3 or 4 times risk of developing RVVC. It is well known that hypersensitive candidal balanitis occurs in men, and it has been postulated that this phenomenon may play a role particularly in RVVC. Women with elevated immunoglobulin E show an increased amount of prostaglandin E2 in vaginal secretions, which is known to enhance *C. albicans* germ tube formation and reduce peripheral blood lymphocyte production.<sup>29</sup> Macrophages and neutrophils are important in protection against systemic invasive candidiasis.<sup>38</sup>

### **Cell-Mediated Immunity**

Cell-mediated immunity (CMI) is the most important host-defense mechanism against mucosal candidiasis. However, the

role of CMI in VVC and RVVC is now questioned because an inflammatory immune response may not be advantageous at a reproductive site.<sup>39</sup> There has always been conflicting evidence about the role of CMI and humoral antibody in RVVC. There may be a more important role for mucosal innate resistance. Recent studies have found that epithelial cells from saliva and vaginal lavages of healthy individuals inhibit the growth of *Candida in vitro*. To date, the evidence suggests that immunity to candidal infections is site-specific, compartmentalized, and involves innate and/or acquired mechanisms from systemic and/or local sources.<sup>40</sup> Studies in rodent models and in humans have emphasized the importance of a compartmentalized local vaginal response rather than a systemic response.

A study in 28 women with RVVC and 25 controls suggested that there was a partial T-cell dysregulation with higher gamma interferon production in RVVC patients. This may be exacerbated by the elevated levels of estrogens in the follicular phase of menstrual cycle. This correlates with the risk of clinical infection during this period.<sup>41</sup>

Some women respond to hyposensitization with *Candida* antigens given over the course of few weeks to months. This indicates a possible role of hypersensitivity reaction in the pathogenesis. Th1- and Th2-type responses cross-regulate each other, and if there is enough increase in antigenic load, there may be an induction of Th2-type response. This could inhibit the normal protection associated with the Th1-type reactivity. There may be a role for immunotherapy involving anticytokine reagents to reduce the Th2-type activity and promote Th1-type activity. Clinically, patients can present as a spectrum of disease, at one end with a hypersensitivity reaction with marked swelling and redness of the vulva associated with low yeast counts, and at the other end, patients who have an anergic response with high yeast counts, obvious vaginal plaques, and minimal edema and reaction.<sup>34</sup>

## CLINICAL DISEASE

### Spectrum of Disease

Candidal infections involve mucous membranes, but can also cause intertrigo, angular cheilosis at the edges of the mouth, paronychia, and onychomycosis (nail infections). In HIV/AIDS patients with immunocompromised status, esophagitis is a common problem; in post-transplant patients or in those with neutropenia, disseminated disease can occur. Although 20% of women carry *Candida* vaginally as a commensal, it is the most common cause of vaginitis in the tropics and it is at least 20 times more common than balanoposthitis.

### Uncomplicated and Sporadic VVC

This is usually caused by *C. albicans* in patients with no underlying predisposing factors including pregnancy. These patients have only mild-to-moderate symptoms.

### Patients Presenting with Vulval and Vaginal Pruritus

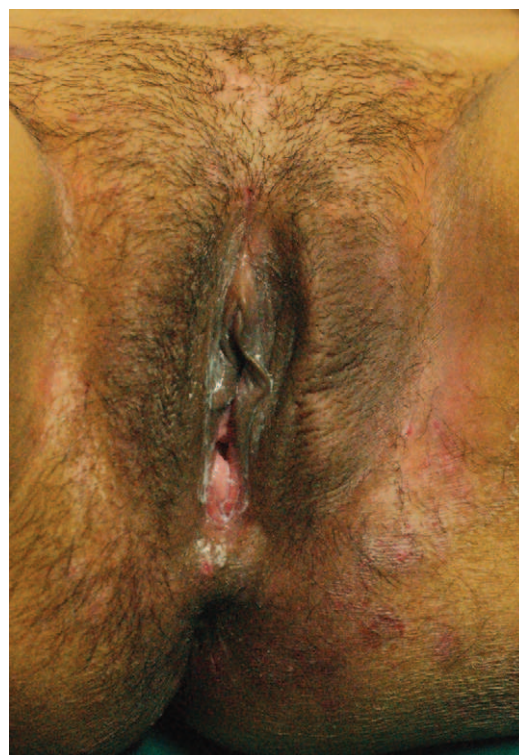
They may notice swelling and redness of the vulva with fissuring, particularly between the intravulval folds with accompanying external dysuria. They may notice a thick white curdy discharge and external dyspareunia. The itching is usually worse at night or after a shower. They often experience most of the symptoms premenstrually or after sexual activity.

On examination, the vulva may be edematous with visible adherent white discharge at the introitus and vestibular area. The vaginal mucosa is brightly inflamed. There may be evidence of acute fissuring or there may be a normal-looking external vulva. On speculum examination, a very inflamed vaginal epithelium with white plaques like 'cottage cheese' may be seen. In some women, there is a more watery or occasionally frank purulent discharge.

### Complicated VVC

This includes recurrent and severe VVC, VVC caused by non-*C. albicans* species, and VVC in women with uncontrolled diabetes, debilitation, or immunosuppression or those who are pregnant (see Table 48.1). RVVC is defined as 4 or more episodes of symptomatic VVC per year (at least one episode confirmed by culture).

There may be a rash with satellite micropustules around the outer labia and redness and involvement of the perianal area (Fig. 48.1). Women with post-thrush vestibulitis may have tender



**Fig. 48.1:** A patient with complicated vulvovaginitis, predisposed by long-term use of broad spectrum antibiotics. Note swelling and erythema of labia and maceration of intertriginous skin.



areas around the hymenal ring particularly between 3 o'clock and 9 o'clock when touched with a white cotton tipped swab. There may be increased redness and increased vascularity on vulvoscopy around the areas of vestibulitis. There may be involvement of the periurethral area and also infection of the urinary tract. In candidal vulvovaginitis, both a clinical and a laboratory diagnosis should be made. In a study on the accuracy of a candidal vaginitis clinical diagnosis, compared with a positive specific DNA probe, it was shown that the clinical diagnosis had a sensitivity of 83.3% and specificity of 84.8%. Despite the use of standardized clinical criteria in this study, diagnosis and therefore treatment may be inaccurate.<sup>42</sup>

## PREDISPOSING FACTORS

Many of these have been mentioned previously including the use of antibiotics, which is usually a short-term risk factor in the first episode, but can also predate RVVC. In one study, the increasing duration of antibiotic use was directly related to an increased prevalence of VVC, and the common indications for antecedent antibiotic use were urinary tract infections and upper respiratory tract disease.<sup>43</sup>

Estrogens are associated with cyclical candidiasis (preperiod). Candidiasis is associated with hormone replacement therapy and also with pregnancy, particularly in the third trimester. The old, high-dose (50 µg) estrogen oral contraceptive pill predisposes to VVC. Progesterone contraceptives and lactation are probably protective.

Estrogen increases the formation of glycogen in epithelial cells, which is a carbon source for yeasts. It also increases the adherence of *Candida* to the epithelial cells and enhances yeast mycelium formation.

In postmenopausal women, there may be underlying risk factors for VVC like hormone replacement therapy, uncontrolled diabetes mellitus, immunosuppression from HIV, broad-spectrum antibiotic therapy, douching, or the use of perfumed, feminine hygiene products.<sup>44</sup> Tamoxifen treatment in postmenopausal women has been found to be associated with RVVC, and in one study, all patients were infected with *C. glabrata*.<sup>45</sup>

General predisposing factors include occlusion and maceration of the skin which is associated with the use of tight, vinyl cycling pants and non-cotton, tight clothing in the tropics.<sup>17</sup> The incidence increases with the onset of sexual activity, the use of sponges, and IUCDs.<sup>23</sup>

Many women with RVVC tend to be atopic. In a study of 95 patients with RVVC and 100 controls, 74% of the patients had allergic rhinitis in comparison to only 42% in the control group. There was no association between RVVC and asthma; however, there was an association with skin test positivity to inhalant allergens and to *C. albicans*. There was a high incidence of family history of allergies in patients.<sup>46</sup>

Among other predisposing factors, the role of iron, vitamin A, and zinc in RVVC is controversial. Unbound iron enhances *C. albicans* growth and iron deficiency has been described with oral

candidiasis. Deficiency of vitamin A may affect keratinization, and protein deficiency affects host defenses. Zinc deficiency (from chronic gut disease or alcoholism) has also been associated with increased oral candidiasis and RVVC.

## VVC IN HIV-SEROPOSITIVE WOMEN

For many years, oral and esophageal candidiasis have been increasingly recognized in HIV-seropositive patients. VVC has also been described in HIV-positive women. This was not surprising with the degree of immunosuppression and the broad-spectrum antibiotic treatments for opportunistic infections in these patients. In effect, RVVC was later described as a presenting marker for underlying HIV infection but is not now thought to be an indication for HIV testing. In a meta-analysis of 39 studies reporting the effect of genital tract infections on the detection of HIV 1, it was found that patients with *Candida* were more likely to have HIV 1 detected (OR 1.8, 95% CI 1.3–2.4).<sup>47</sup>

A study assessing the effect of treatment of vaginal infections on the shedding of HIV in 98 patients with VVC showed that the vaginal HIV 1 RNA decreased after treatment for candidiasis. *Trichomonas vaginalis* treatment showed the same finding but this was not the case for BV. Treatment of VVC resulted in a 3.2-fold reduction in the concentration of HIV in vaginal secretions and a 3-fold decrease in the likelihood of detecting HIV 1 infected cells.<sup>48</sup>

In another prospective study on 205 HIV-positive women, it was shown that the risk of developing symptomatic VVC increased 6.8 times for women with CD4+ cell count less than 200 cells/µL.<sup>49</sup> Another study looking at oropharyngeal candidiasis showed that oral disease presents earlier in HIV-seropositive patients with higher CD4+ cell count compared to those with VVC. This study also suggested that the protection against oropharyngeal candidiasis or VVC was more dependent on factors in the local mucosal immune milieu than systemic CMI.<sup>41</sup>

## LABORATORY INVESTIGATIONS

### pH Measurement

The pH of vaginal discharge in VVC is low, between 3 and 4.5, which distinguishes it from other causes of vaginitis. Swabs should be taken from the lateral vaginal wall and placed on the pH paper. Contamination with blood, cervical mucus, semen, and local medications, e.g., antifungal creams, should be avoided as it may affect the pH of the secretions.

### Microscopic Examination

Wet mount of saline preparation should be routinely done to exclude clue cells and trichomonads. A sample of vaginal secretion is taken with a loop and mixed into a drop of saline on one slide and a drop of 10% KOH on another, cover slips placed on top and viewed under low-power microscopy. In 40–60% patients, budding yeasts and lengths of pseudohyphae may be seen.

## Culture

The majority of symptomatic patients will have high counts more than  $10^3$  blastospores per mL of vaginal secretion. Swabs from the lateral wall of the vagina can be placed in Amies transport medium or can be directly plated on a Sabouraud plate. In patients who have small number of yeasts because of partial treatment or in those who are hypersensitive to small amounts of antigen, the yield can be improved by taking vaginal washings or inoculating swabs directly into a broth media with antibiotics. Wherever possible, cultures should always be done to confirm the diagnosis, particularly if there is a negative wet preparation examination. Cultures may be necessary in complicated disease, where non-*C. albicans* strains are suspected and where sensitivity testing against antifungals is necessary.

New chromogenic agar media for the differentiation of *Candida* species are useful in situations where mixed infections are suspected or there is inadequate response to usual therapy (Fig. 48.2).<sup>50</sup>

## Cervical Smear (Pap Smear)

A study on the clinical significance of detecting *Candida* on Pap smears showed that there was marked inflammation associated with symptomatic disease, but no association with the type of yeast seen (blastospores or hyphae) or number of *Candida* organisms present.<sup>51</sup>

## Polymerase Chain Reaction (PCR)

It has been suggested that recovery of fewer than 10 yeast colonies from a vaginal swab is unlikely to be pathognomonic for symptomatic candidiasis. Enrichment broth cultures for *Candida* may be over-sensitive and fail to distinguish between

the true infection and commensal carriage in most cases. Thus, PCR, a highly sensitive laboratory test, has little value in the diagnosis of uncomplicated candidal vulvovaginitis.<sup>52</sup>

In a study of 50 women with RVVC and 45 women with one or less episodes of vaginitis, it was shown that *Candida* was more easily detectable in those with RVVC even when they were asymptomatic. The culture, wet mount and Gram stain, had a sensitivity of 66.6% in comparison with PCR.<sup>53</sup> One hundred and four women with RVVC had vaginal secretion cultured and tested by PCR. Culture was positive in 31 women (29.5%) and 44 women (42.3%) had a positive PCR for *Candida* species. In 13 women (12.5%), only PCR was positive.<sup>54</sup>

The isolation of yeasts between sexual partners using PCR has revealed identical strains in 8 out of 15 couples.<sup>55</sup> *C. albicans* DNA in serum has been measured by PCR for the diagnosis of invasive candidiasis and PCR with dot blot hybridization has been used to identify rare *Candida* species and other yeasts.

## DIFFERENTIAL DIAGNOSIS OF CLINICAL CANDIDIASIS

At the initial presentation in the sexually active patient, it is essential to screen for all causes of discharge, including upper genital tract infection by taking cervical swabs for Chlamydia, gonococci and, if indicated, herpes. Also, there should be exclusion of other causes including BV and trichomoniasis by suitable laboratory tests. Although the pH and microscopy may often exclude these, there are often mixed infections with mixed signs and symptoms, so full screening including culture for *T. vaginalis* is preferred. In fact, BV is quite commonly found in patients with RVVC.

The differential diagnosis of RVVC includes infective causes, like recurrent BV, recurrent trichomoniasis, unrecognized recurrent genital herpes, suprapubic lice, genital scabies and non-infective causes like, allergic and chemical vulvitis, contact dermatitis, atrophic vaginitis, atrophic vestibulitis, idiopathic vestibulitis syndrome, desquamative inflammatory vaginitis, erosive lichen planus, lichen sclerosus, dermatoses (eczema, atopy, psoriasis), and physiologic leucorrhoea.<sup>55</sup>

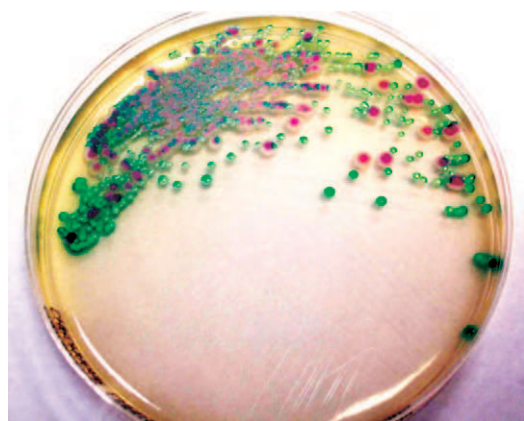
## MANAGEMENT

### Uncomplicated VVC

Many regimens have been recommended in various guidelines (Table 48.2).<sup>56–59</sup>

Most women have uncomplicated disease with cure rates with antifungal medications of more than 80%. Local imidazole treatments in the forms of ovules, pessaries, tablets, creams for one, three, or six days have relatively equal efficacy. However, instant treatment does not work instantly. These preparations probably stay inside the vagina for some days. External cream is useful if external genitalia are involved.

In moderate cases with severe edema and fissuring, there may be a period of 1–2 weeks before all symptoms get resolved. The area can be quite extensive and the patient should be advised to rest



**Fig. 48.2:** Use of *Candida* chromogenic media (CHROMagar™). Inoculated with *C. albicans*, green colonies; *C. krusei*, flat pink colonies; *C. tropicalis*, blue colonies after 48 hours incubation; other *Candida* species—white to pink. (Mycology preparation & photography by Karen Rogers and Wendy McKinney. Mycology Reference Laboratory, LAB+ Auckland Hospital, New Zealand).

**Table 48.2:** Recommended Regimens for Uncomplicated Vulvovaginal Candidiasis

<b>A. CDC Guidelines (2010)<sup>10</sup></b>
<i>Over the Counter Intravaginal Agents</i>
Butoconazole 2% cream 5 g intravaginally daily for 3 days, or
Clotrimazole 1% cream 5 g intravaginally daily for 7–14 days, or
Clotrimazole 100 mg vaginal tablet daily for 3 days, or
Miconazole 2% cream 5 g intravaginally for 7 days, or
Miconazole 4% cream 5 g intravaginally for 3 days, or
Miconazole 100 mg vaginal suppository, one suppository for 7 days, or
Miconazole 200 mg vaginal suppository, one suppository for 3 days, or
Miconazole 1200 mg vaginal suppository, one suppository for 1 day, or
Tioconazole 6.5% ointment 5 g intravaginally in a single application.
<i>Prescription Intravaginal Agents</i>
Butoconazole 2% cream (single dose bioadhesive product), 5 g intravaginally for 1 day, or
Nystatin 100,000-unit vaginal tablet, one tablet for 14 days, or
Terconazole 0.4% cream 5 g intravaginally for 7 days, or
Terconazole 0.8% cream 5 g intravaginally for 3 days, or
Terconazole 80 mg vaginal suppository for 3 days
<i>Oral Agent</i>
Fluconazole 150 mg oral tablet, one tablet in a single dose
<b>B. WHO Guidelines (2003)</b>
Miconazole or clotrimazole, 200 mg pessary intravaginally daily for 3 days, or
Clotrimazole, 500 mg pessary intravaginally in a single dose, or
Fluconazole, 150 mg orally as a single dose.
<i>Alternative regimen</i>
Nystatin, 100,000 unit vaginal tablet, one tablet daily for 14 days
<b>C. UK National Guidelines on the Management of Vulvovaginal Candidiasis (2007)</b>
Clotrimazole, pessary, 500 mg stat <sup>†</sup>
Clotrimazole, pessary, 200 mg x 3 nights <sup>†</sup>
Clotrimazole, pessary, 100 mg x 6 nights <sup>†</sup>
Clotrimazole, vaginal cream, (10%) 5 g stat <sup>†</sup>
Econazole, pessary, (ecostat 1) 150 mg stat <sup>†</sup>
Econazole, pessary, 150 mg x 3 nights <sup>†</sup>
Fenticonazole, pessary, 600 mg stat <sup>†</sup>
Fenticonazole, pessary, 200 mg x 3 nights <sup>†</sup>
Isoconazole, vaginal tablet, 300 mg x 2 stat <sup>†</sup>
Miconazole, ovule, 1.2 g stat <sup>†</sup>
Miconazole, pessary, 100 mg x 14 nights <sup>†</sup>
Nystatin, vaginal cream, (100,000 units) 4 g x 14 nights
Nystatin, pessary, (100,000 units) 1–2 x 14 nights
<i>Oral Therapies</i>
Fluconazole, capsule, 150 mg stat <sup>§</sup>
Itraconazole, capsule, 200 mg bd x 1 day <sup>§</sup>
<i>Treatment of Recurrent Vulvovaginal Candidiasis</i>
Induction, Fluconazole, § 150 mg capsule every 72 hours x 3 doses
Maintenance, Fluconazole, § 150 mg capsule once a week for 6 months
<i>Alternatively</i>
Induction topical imidazole therapy can be increased for 10–14 days
Maintenance:
Clotrimazole, 500 mg, pessary, once a week
Fluconazole, § 50 mg capsule daily
Itraconazole, § 50–100 mg capsule daily
Ketoconazole, § 100 mg capsule daily
<b>D. European STD Guidelines (2001)</b>
<i>Topical Therapies</i>
Clotrimazole, vaginal tablet 500 mg once or 200 mg once daily for 3 days, or
<i>Oral Therapies</i>
Fluconazole, 150 mg as a single dose, or
Itraconazole, 200 mg twice a day for one day.

<sup>†</sup>Over-the-counter preparations.<sup>†</sup>Effect on latex condoms and diaphragms not known.<sup>†</sup>Product damages latex condoms and diaphragms.<sup>§</sup>Avoid in pregnancy/risk of pregnancy and breastfeeding.

the “injured limb” and avoid sexual activities. Otherwise, relapse can occur requiring more prolonged courses of local antifungal therapy. Often, systemic (oral) therapy such as single dose of 150 mg of fluconazole, repeated after 3 days or itraconazole 200 mg a day for 2 days helps.

## Complicated VVC

Before initiating pharmacotherapy, every effort should be made to eliminate underlying or predisposing factors when recognized.<sup>58</sup> In patients with diabetes, hyperglycemia should be controlled. However, cessation of oral contraceptive pills rarely results in reduction of frequency of clinical episodes. Removal of IUCDs is of variable use and not indicated. In women with RVVC precipitated by frequent use of systemic antibacterial agents, it is unnecessary to put the patient on long-term maintenance regimen and individual episodes can be prevented by the use of episodic prophylactic azole agents in conjunction with the needed antibacterial course.<sup>58</sup> Unfortunately, in the majority of the patients with RVVC, no underlying precipitating factor is evident. Identifying the species of the yeast present and exclusion of mixed yeast infections (10%) are necessary. Patients with non-*C. albicans* species should be managed accordingly (see below).

Each case of RVVC should be treated with an initial induction therapy followed by a maintenance regimen. The 2006 CDC Guidelines<sup>10</sup> for treatment of RVVC recommend a short course of oral or topical azole therapy to treat each individual episode. Many specialists recommend a longer duration of initial induction therapy (e.g., 7–14 days of topical therapy or a 150 mg, oral dose of fluconazole repeated 3 days later) to achieve mycologic remission before initiating a maintenance regimen. A multicenter double-blind study of initial induction therapy in 565 women with complicated VVC has shown that 150 mg fluconazole given stat, then repeated three days apart was adequate to achieve control. Women with recurrent, but not severe, infection responded well to a single dose of 150 mg fluconazole.<sup>60</sup>

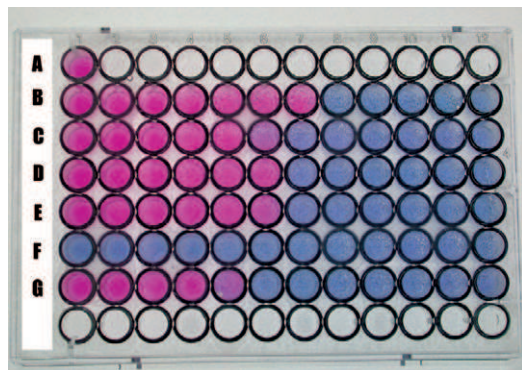
Sobel's multicenter, prospective, randomized study on maintenance fluconazole therapy for RVVC on 387 women, half on placebo, used the induction of 150 mg fluconazole, 72 hours apart. This was followed by 150 mg pulses weekly. At 6 months, 90.8% were disease free (35.9% –placebo group); at 9 months, 73.2% (27.8%); and 12 months, 42.9% (21.9%).<sup>61</sup>

A recent study used an induction dose of 600 mg of fluconazole in 117 women, then a dosage of 200 mg weekly for 2 months, then 200 mg every 2 weeks for 4 months, and 200 mg monthly for 6 months. One hundred and one women (90%) were disease free at 6 months and 80 (77%) after 1 year.<sup>62</sup>

Based on available data, therapy for VVC in HIV-infected women should not differ from that for seronegative women. Fluconazole, 200 mg weekly dose as a prophylactic therapy is not recommended for routine primary prophylaxis in HIV-infected women in the absence of RVVC.

Failure of these regimens regardless of the duration of treatment occurred with non-*C. albicans* species. If these species are isolated, full-sensitivity assessment should be carried out so that dosage





**Fig. 48.3:** Sensititre minimum inhibitory concentration plate showing sensitivity of *C. glabrata* isolate to six antifungals. (NCCLS reference method for broth dilution antifungal susceptibility testing of yeasts). Red—positive growth; blue—negative growth. A, Growth control; B, Amphotericin B, 1.0 (sensitive); C, Fluconazole, 16 (dose dependant); D, Itraconazole, 0.5 (dose dependent); E, Ketoconazole, 0.5 (sensitive); F, 5-flucytocine, 0.03 (sensitive); G, Voriconazole, 0.25 (sensitive).

can be tailored accordingly (Fig. 48.3). A two-week regimen can be tried on increased dosage, e.g., 450 mg daily.

#### Fluconazole Resistance in RVVC

Fluconazole-resistant strains of *C. albicans* are rare in VVC. Fluconazole-resistant infection can occur more frequently in immunosuppressed patients with oropharyngeal and esophageal candidiasis. Fluconazole resistance may be due to the drug being expelled through the membrane channels.

#### VVC and RVVC in Pregnancy

The oral imidazoles are contraindicated in pregnancy. There is evidence of teratogenicity from the long-term use of high dose of fluconazole.<sup>63</sup> Hypoplastic left heart syndrome was found to be an increased risk (OR 2.30; 95% CI 1.04, 5.06) in 7 cases out of 176 pregnant women on antifungal drugs (4581 controls). Three had used miconazole, 1 terconazole, 1 ketoconazole, and 2 antifungal unknown.<sup>64</sup> Extended courses of topical azoles (10–14 days) are usually effective in problematic cases. RVVC sometimes disappears in pregnancy, but in some women, it may persist. The use of clotrimazole pessaries, 500 mg intravaginally every one or two weeks can control symptoms.

#### Non-*C. albicans* VVC

*C. glabrata*, (a small, non-budding yeast) is the second most common yeast associated with RVVC and is 10–100 folds less susceptible to all azoles.<sup>55</sup> Many strains have a higher minimum inhibitory concentration and may respond to higher dosages of oral antifungals. *C. glabrata* along with *C. tropicalis* may be resistant to fluconazole, predominately in HIV positive women.<sup>65</sup> The only drug more active against *C. glabrata* than *C. albicans* is flucytosine. Intravaginal boric acid, 600 mg/day for 14 days will result in eradication of *C. glabrata*

in approximately 70% of patients.<sup>66</sup> Flucytosine as a 17% solution, given intravaginally, is a good alternative.

On microscopy *C. tropicalis* appears as ellipsoidal budding cells with plenty of pseudomycelia, which are poorly branched. It is found increasingly in patients with impaired immunity and has variable sensitivity to fluconazole.

*C. krusei* is inherently resistant to fluconazole.<sup>67</sup> On microscopy, it has budding cells, which are ellipsoidal to cylindrical; pseudomycelium is often present.

#### New Developments in Antimycotic Agents

The absorption of the capsule formulation of itraconazole is variable especially with hypochlorhydria, but swallowing with non-diet Coca Cola may help. The new itraconazole cyclodextrin oral solution with better absorption has similar clinical response rates to fluconazole when it is being used in Candida esophagitis in HIV infection.<sup>65</sup> The cost of this preparation has precluded its use in RVVC. Similarly, the new azole anti-fungal agent, voriconazole, is highly expensive. Voriconazole blocks the sterol biosynthesis and alters the morphology of Candida species and has been shown to be more effective against non-*C. albicans* strains as well as fluconazole-resistant *C. albicans*. Fifteen women suffering from acute VVC and 17 from RVVC showed a clinical cure of 66% and mycological cure of 75% at one month, using oral posaconazole one 200 mg dose.<sup>68</sup>

#### Other Treatments

A randomized, double-blind, placebo-controlled study of 55 women with VVC treated with 150 mg fluconazole followed by either 2 capsules of placebo or 2 capsules of probiotic daily (a mixture of lactobacilli) for 4 weeks had less discharge and other symptoms and less culture-positive yeasts on follow-up.<sup>69</sup>

In another study, agar dilution tests were performed to assess the antifungal potential of boric acid on fluconazole-sensitive and fluconazole-resistant *C. albicans*. Minimum inhibitory concentrations ranged from 1563 to 6250 mg/L, i.e., concentrations available vaginally and boric acid showed a fungistatic to fungicidal effect.<sup>70</sup>

#### Important Considerations

- The non-*C. albicans* strains of yeasts are identified using biochemical tests, e.g., API 20C, Bio Merieux. Determination of minimum inhibitory concentration is recommended using a microbroth dilution method with interpretive break points, as in the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS).<sup>71</sup> A quantitative reverse transcriptase-PCR-based azole sensitivity test has been developed to test for *C. glabrata* resistance to azoles.<sup>72</sup> Multi-azole cross-resistance can occur in these isolates. These have been particularly described in HIV-positive patients with reduced CD4+ counts (less than 50 cells/mL).

- Terconazole cream (available in the US) has been recommended as first-line treatment for non-*C. albicans* vaginal infections. In one study on 20 patients, 14 (56%) had mycological cure.<sup>73</sup>
- Non-*C. albicans* VVC has been treated with boric acid powder in a double-blind trial using daily intravaginal gelatin capsules with 600 mg of boric acid versus identical capsules with 100,000 units of nystatin for 14 days. Cure rate with boric acid capsules was 72% at 30 days, whereas with nystatin, it was 50%. Blood boron analysis indicated little absorption from the vagina with blood concentrations of less than 10 µg/L during the use of one or two boric acid capsules per day. Boric acid powder was used because boric acid crystals occasionally cause male dyspareunia.<sup>74</sup>
- Maintenance therapy with topical boric acid was compared with oral itraconazole in the treatment of RVVC in a prospective non-randomized study. The response to treatment was the same in both groups. After 6 months, the therapy was discontinued, and at the 12th month visit, 54% had relapsed.<sup>75</sup> The toxicity profile of long-term maintenance therapy of boric acid is unknown.
- *S. cerevisiae* has variable sensitivity to antifungals.<sup>76</sup>
- Strains resistant to oral azoles, can be treated with boric acid or nystatin vaginal cream (100,000 units nocte as pessaries). Aqueous gentian violet 1% has also been used in resistant cases.<sup>77</sup> Topical flucytosine has been described as being useful in some cases and a formulation mixed with amphotericin B for the use in refractory VVC caused by *C. glabrata* has been described.<sup>78</sup>

## Oral Azoles—Systemic Toxicity, and Drug Interactions

Maintenance dose therapy with oral azoles, such as itraconazole and fluconazole, works because of the prolonged half-life (4–5 days) of these drugs on usual dosage regimens. These triazoles have been associated with clinically significant drug interactions. Itraconazole and fluconazole in high doses are inhibitors of cytochrome (CYP) P3A4. These cytochrome P-450 enzymes are a family of catalytic hemoproteins that are important in the metabolic transformation of many drug substrates. Reduced CYP activity results in decreased metabolism of the substrate drug with an increase in the bioavailability and potential drug toxicity.

Care should be taken if high doses of fluconazole are mixed with drugs with extensive first-pass metabolism such as astemizole, cisapride, or drugs with a narrow therapeutic window, such as warfarin, digoxin, phenytoin, and sulfonylureas. Care should be taken when itraconazole is prescribed with hepatotoxic drugs. Life-threatening cardiac arrhythmias might follow the combined use of high-dose fluconazole or itraconazole, and astemizole, cisapride; and the new generation H1 antihistamines. Other drugs requiring monitoring include cyclosporine, felodipine, and quinidine.<sup>79</sup>

## Acute Candidal Balanoposthitis

Balanitis occurs in about 10% of male genitourinary clinic attendees; the most common cause is candidiasis. The foreskin is often involved in the uncircumcised men.

### CLINICAL PRESENTATION

#### Symptoms

The patient may complain of a rash involving the glans penis or the prepuce, which is itchy, swollen, and red. Occasionally, there may be some discharge, mild dysuria, and dyspareunia. Symptoms may occur within an hour of sexual activity (hypersensitivity reaction) or within 24–48 hours post-exposure (candidal infection). This may be a relapsing recurrent condition, which can be disquieting for the patient. It is often acquisition from an infected female partner or be secondary to a low-grade skin condition, i.e., eczema or seborrheic dermatitis.

#### Signs

There may be erythema and swelling with a macular/papular rash of the glans penis and foreskin and superficial ulceration. A white subpreputial discharge, increased skin markings, fissuring of the glans and foreskin, and occasionally regional lymphadenopathy may be present.

### INVESTIGATIONS

A swab can be taken from the subpreputial area, glans, or urethra, and spread on a slide for a gram stain. It can be sent in transport medium or inoculated immediately onto Sabouraud dextrose media. It is wise in certain populations and age groups to do a urine analysis for glucose.

Where there is excessive fissuring or painful ulcers, a swab for herpes should be taken. Likewise, if the ulcerations are really atypical, a dark-ground examination for treponemes or smear and culture for *Haemophilus ducreyi* should be considered.

### MANAGEMENT

Non-specific balanoposthitis can be part of low-grade skin disorders like seborrheic dermatitis and contact allergy with colored or perfumed agents where *Candida* can be opportunistic.

Therefore, salt-water baths (1 pint of warm water to a teaspoon of ordinary salt) twice daily are recommended along with avoidance of soaps and bath additives.

Clotrimazole cream, 1% can be applied locally twice a day for at least a week. A 1% hydrocortisone and antifungal cream, like miconazole, can also be used. Alternatively, fluconazole 150 mg capsule/tablet orally stat can be advised if patient is allergic to imidazoles. This eradicates infection of the urethral meatus, inaccessible by creams or nystatin cream.

In patients, where contact allergic dermatitis is suspected, aqueous cream as soap substitute should be prescribed.

NB: If balanoposthitis persists for more than 6 weeks, a biopsy should be considered to exclude other causes including penile intraepithelial neoplasia, Zoon's balanitis (plasma cell balanitis), or erythroplasia of Queyrat.

### Summary

Vulvovaginal candidiasis is a common, debilitating genital condition that is often misdiagnosed and poorly managed. In recurrent disease, diagnosis of the yeast involved, as well as exclusion and treatment of any underlying condition is essential. Although preparations of local antifungals are many; they all have similar efficacy. Systemic antifungals are few and sometimes non-*C. albicans* strains are resistant to them, requiring further laboratory evaluation. Candidal Balanoposthitis, especially when recurrent, can be perplexing and upsetting. Reassurance and exclusion of underlying conditions, where possible, is important, although short-term local therapy of an antifungal and low-dose hydrocortisone mixture is usually effective.

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# Trichomonas Vaginalis Infections

Barbara Van Der Pol

# 49

## Introduction

*Trichomonas vaginalis* is a sexually transmitted protozoan parasite that invades genital epithelia and may cause trichomoniasis in women and urethritis in men. The World Health Organization estimates that approximately 174 million cases of trichomoniasis occur globally each year.<sup>1</sup> This is more than the estimated number of chlamydial and gonococcal infections combined. Approximately 7–8 million cases are estimated to occur annually within the US alone. These estimates are for overt, symptomatic disease and cannot account for asymptomatic infections. Although this pathogen is recognized as a sexually transmitted infection (STI), unlike infections caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*, reporting of trichomonas is not required by public health entities such as the Centers for Disease Control and Prevention.<sup>2</sup> As a result of this lack of reporting, it is difficult to estimate the actual prevalence of *T. vaginalis* infection.

This highly prevalent pathogen predominately affects women and may play a role in development of upper genital tract complications and cervical cancer, lead to adverse outcomes of pregnancy, and increase risk of HIV acquisition or transmission. Public health practitioners need to be aware of the likelihood of co-infection with other STIs, diagnostic test performance, and the appropriate treatment strategies in order to manage patients effectively. Each of these aspects of *T. vaginalis* will be presented in detail in the following sections.

## Biology and Pathogenesis

*T. vaginalis* is a flagellated protozoan that is highly motile (Fig. 49.1). Trichomonads, which are approximately the size of lymphocytes (15–25  $\mu\text{m}$  in length), have several long flagella that are involved in motility as well as an undulating membrane on one side of the organism that is clearly visible with light microscopy. *T. vaginalis* is strictly anaerobic and can survive in a variety of pH conditions ranging from highly acidic (pH 3.5), which is common during bacterial vaginosis, to basic (pH 8.0). As a result of sensitivity to atmospheric oxygen, drying conditions, and temperatures below 35°C, *T. vaginalis* does not survive *ex vivo*

for extended periods (greater than a few hours). Organisms lose motility quickly at room temperature.<sup>3</sup> Therefore transmission by means other than sexual contact is rare.

Upon entry into the vaginal milieu, *T. vaginalis* encounters the mucous layer that is the first line of defense from microbial colonization. Trichomonads produce enzymes that degrade mucin, the major component of mucous, thus allowing the organisms to come into contact with the cells of the vaginal epithelium.<sup>4</sup> Trichomonas also produces adhesins that enable attachment of the pathogen to the cell surface of vaginal epithelium. These adhesins are upregulated during times of high iron concentration. This mechanism may allow trichomonads to remain adhered to cells during menses.<sup>5</sup> Contact with epithelial cells results in their destruction and recruitment of inflammatory cells to the vagina, resulting in vaginal discharge. However, there are many factors that influence the level of cytotoxicity and local immune response. As a result, infection can cause a range of outcomes from completely asymptomatic disease to heavy discharge, odor, and itching.

Trichomonads themselves are susceptible to infection by a double stranded RNA virus that may influence the virulence of



**Fig. 49.1:** *T. vaginalis* from *in vitro* culture. Trichomonads stained with Giemsa stain (from [www.cdc.gov](http://www.cdc.gov)). Arrows show the flagella and asymmetrically located undulating membrane.

trichomonas.<sup>6</sup> Studies have shown that this virus is present in as many as 75% of patient isolates obtained from STD clinic attendees,<sup>7</sup> suggesting that the virus-infected trichomonas may have a survival advantage when in humans. Interestingly, isolates with the virus may be less likely to be resistant to metronidazole.<sup>8</sup>

Trichomonas is capable of phagocytosis of microbes commonly found in the vaginal environment including lactobacilli<sup>9</sup> and *Mycoplasma hominis*.<sup>10</sup> Lactobacilli are known to play a key role in vaginal health, while *M. hominis* has been linked with vaginal and cervical discharge syndromes as well as upper genital tract complications. The impact of interaction between *T. vaginalis* and these organisms is unknown. For an excellent review of the biology of trichomonas see Petrin and colleagues.<sup>11</sup>

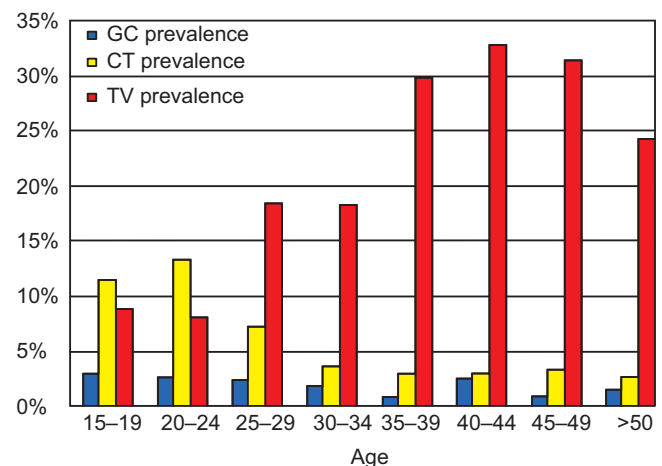
## Epidemiology

The epidemiology of trichomonas is poorly understood for several reasons. First, since this infection is not monitored by public health agencies, there are few sources of reliable, population-based data. In studies that have reported testing in both men and women, the prevalence in women is 4–5 fold higher than in men. Second, despite evidence to the contrary, trichomonas infection is commonly believed to result in symptomatic disease in women although it is recognized that men rarely have overt disease.<sup>12</sup> Asymptomatic infection is widely considered to be a nuisance rather than a threat to reproductive health so screening in asymptomatic populations is uncommon. Thus, the majority of people tested for trichomonas are women with symptoms or attending an STD clinic that routinely provides such testing. Additionally, prevalence data are available from studies of HIV and STI studies in resource-constrained areas of the world such as sub-Saharan Africa. As a result, reports of trichomonas prevalence may represent populations at elevated risk (i.e., symptomatic women or women from STI endemic regions of the world) and should be considered in the appropriate context. Finally, as will be described below, the diagnostic methods used to identify trichomonal infection vary widely in sensitivity. Use of insensitive tests results in under-reporting of infections. For those women who are evaluated for the presence of *T. vaginalis*, as many as 50% of cases may be missed depending on the diagnostic method used. This lack of detection of infection would suggest that in some cases, even in high-risk populations, the prevalence may be significantly under-reported. Therefore, despite reports of prevalence ranging from 2 to 47%, it is unclear whether these estimates over- or under-represent the true prevalence of trichomonas within generalized populations.

Studies of the epidemiology of *T. vaginalis* infection have described risk factors similar to those identified for other STIs (for review see Johnston and Mabey<sup>13</sup>). These include infection with other STIs, previous infection with *T. vaginalis*, lower socioeconomic status, residence in a correctional facility, and sexual behaviors that increase risk of infections. These behaviors include

higher numbers of sexual partners, inconsistent condom use, sex in exchange for money or drugs, and intravenous drug use. Patients with any of these risk factors should be considered for evaluations of infection with trichomonas. Higher prevalence rates have often been reported in Black compared to White populations in the US; however, race is likely to be a surrogate for underlying factors in these studies. Finally, unlike the classic age distribution seen with *C. trachomatis*, and to a less dramatic degree with *N. gonorrhoeae*, *T. vaginalis* prevalence appears to increase with age.<sup>14</sup> In a multisite study performed in the US using DNA-based diagnostic testing, the peak age for infection was 40–44 years (Fig. 49.2).<sup>15</sup> A large, retrospective population-based study in China also demonstrated peak prevalence in women aged 35–45 years.<sup>16</sup> The difference in age-specific prevalence rates may be an artifact of long-term carriage and under-diagnosis of trichomonas that results in a cumulative prevalence rate. If untreated long-term infection were the only cause of increased age-specific prevalence, this would predict a steady increase throughout all age groups. However, all studies that have examined age have found that prevalence rates decline after age 50. Changes in prevalence may be related to changes in susceptibility as a result of hormonal or other changes in the vaginal micro-environment as women age. More research is clearly needed to improve our understanding of the biological factors that may affect women's risk of infection with *T. vaginalis*.

The most informative estimate of prevalence and risk factors in the United States was collected as part of a study of adolescent and adult health in a nationally representative sample of people



**Fig. 49.2:** Age-specific prevalence of *C. trachomatis*, *N. gonorrhoeae* and, *T. vaginalis*. The age-specific prevalence for *C. trachomatis* (CT), *N. gonorrhoeae* (GC), and *T. vaginalis* (TV) are shown from a multisite study of 1923 women. Gonorrhea rates are slightly higher in young women while chlamydia rates show the typical pattern of a definite peak for women less than 30. In the same women, trichomonas infection peaked in 35–50 year olds.



**Table 49.1:** Epidemiologic Risk Factors for *T. vaginalis* Infection in Women\*

	Category	Prevalence (98% CI)	P
Age (years)	14–19	2.1 (1.3–3.4)	0.076
	20–29	2.3 (1.3–4.0)	
	30–39	4.0 (2.5–6.5)	
	40–49	3.6 (2.3–5.7)	
Race	Non-Hispanic White	1.3 (0.7–2.3)	<0.001
	Non-Hispanic Black	13.3 (10.0–17.7)	
	Other	2.7 (0.9–8.3)	
Education	Less than high school	6.3 (4.4–8.9)	<0.001
	High school	4.7 (1.2–3.0)	
	More than high school	1.9 (1.2–3.0)	
Poverty index ratio	0–1.85	5.4 (3.6–8.2)	<0.001
	1.851–3.5	2.7 (1.7–4.4)	
	>3.5	0.9 (0.5–1.9)	

\*Adapted from Sutton MY, Sternberg M, Koumans EH, et al.<sup>18</sup>

aged 14–49 (NHANES). From this data set the prevalence rates of *C. trachomatis*, *N. gonorrhoeae*,<sup>17</sup> and *T. vaginalis*<sup>18</sup> in women were estimated to be 2.5% (95% CI 1.8–3.4%), 0.3% (95% CI 0.2–0.4%), and 3.1% (95% CI 2.3–4.3%), respectively. The strengths of these data are the large sample size (2000–3500 participants), the representative sampling design and the use of highly sensitive DNA-based diagnostic testing for all three organisms. These data support the global estimates that describe the prevalence of trichomonas as higher than that of chlamydia and gonorrhea combined. Table 49.1 lists epidemiologic risk factors for *T. vaginalis* infection in women.

Given the shared mechanism of transmission, it is not surprising that *T. vaginalis* infection often occurs with other STIs and reproductive tract infections (RTI) such as bacterial vaginosis (BV), and yeast (*Candida*) infection. Similar to prevalence rates, co-infection rates are available only as rough estimates as a result of limited data available that include testing for all organisms and due to the poor performance of microscopy for detection of trichomonas in women with other vaginal or cervical infections. Clue cells, epithelial cells with distinctive microscopic appearance that are indicative of BV, and lymphocytes that are a major component of discharge are both similar in size to trichomonads and may obscure motility. As a result, BV and yeast infections that are concurrent with trichomonal infections may hinder diagnosis of *T. vaginalis*. Women who are tested for STI, BV, or yeast infections should be evaluated for the presence of trichomonas and this evaluation may require more sensitive diagnostic methods than microscopy.

## HIV and Trichomonas

The relationship between HIV and discharge-causing STI is complex and bi-directional. Frequent co-infection of *T. vaginalis* with other STI and RTI and the shared mode of transmission add to the difficulty of understanding the exact effect of *T. vaginalis* on the risk of HIV acquisition and/or transmission.<sup>19</sup> Interestingly,

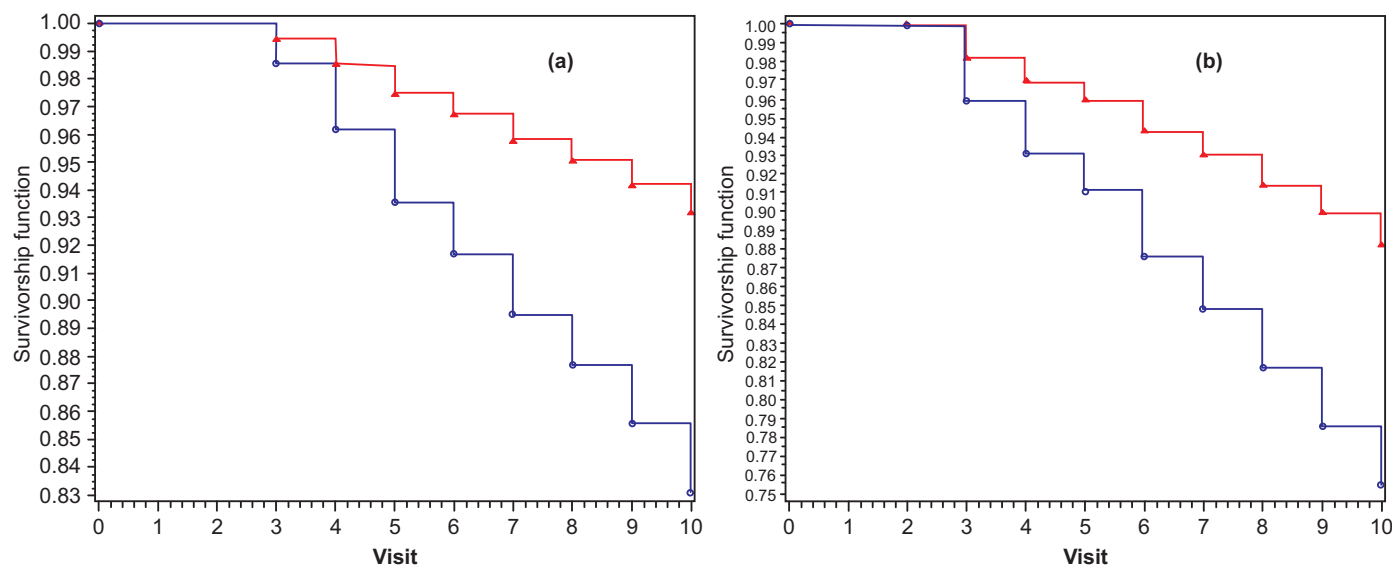
although little attention has been paid to trichomonal infection in men in the US, one of the first studies to identify a significant association between HIV and trichomonas was performed in men. Genital viral load has been shown to be one of the most important factors in predicting risk of HIV transmission within discordant couples. In men with symptomatic urethritis, *T. vaginalis* was significantly linked to increased concentrations of HIV in seminal plasma ( $p = 0.022$ ).<sup>20</sup> Men with trichomonas identified using DNA-based tests had six-fold increase in the concentration of HIV in semen compared to men without trichomonas. Similarly, in a prospective study of 203 HIV-positive women, treating *T. vaginalis* led to a 4.2-fold reduction in cell-free HIV viral load ( $p < 0.001$ ).<sup>21</sup> These results indicate seropositive men and women should be screened and treated for *T. vaginalis* infection in order to reduce HIV transmission to their sexual partners.

In a longitudinal study of women recruited from family planning clinics in Uganda and Zimbabwe, *T. vaginalis* was found to be more prevalent among HIV positive women than among matched controls (11.3% vs. 4.5%,  $p = 0.002$ ).<sup>22</sup> Moreover, HIV-negative women receiving a diagnosis of *T. vaginalis* were nearly 3 times more likely to become infected with HIV within the following 3 months than women without trichomonas (adjusted OR 2.74; 95% CI, 1.25–6.00). These data were from a general population of women and support the findings of other studies in populations consisting primarily of female sex workers.<sup>23,24</sup>

Mathematical modeling has derived similar risk estimates for HIV susceptibility and transmission.<sup>25</sup> The analysis estimated that *T. vaginalis* infection increases a woman's risk for HIV infection by 2–3 fold and is suspected to have had a huge impact on the HIV pandemic by increasing viral shedding in HIV-infected individuals and inflammation or micro-abrasions in genital tissues that enlarge HIV entry portals in HIV-negative partners (Fig. 49.3). Findings from the model of HIV transmission estimated the annual economic burden for trichomoniasis-attributable HIV cases to be \$167 million. This analysis demonstrates the interaction between high prevalence rates and a modest, but significant, increase in risk. While the effect on HIV risk of *T. vaginalis* infection cannot be altered, prevalence can, and must, be reduced by improved efforts to control this pathogen, particularly in populations at high risk for HIV infection.<sup>26,27</sup>

## Clinical Manifestations

Though often considered merely a nuisance, *T. vaginalis* infection in men is known to be an important cause of urethritis, prostatitis, and potentially male factor infertility.<sup>12,28</sup> Krieger et al. (1993) demonstrated an association between *T. vaginalis* and sexually transmitted non-gonococcal/non-chlamydial urethritis among a population of sexually active men.<sup>29</sup> Several studies have found *T. vaginalis* to be a common cause of urethritis in men.<sup>20,30–32</sup> Typical clinical practices do not include routine screening for trichomoniasis in men, even those who are symptomatic.<sup>33</sup> This is, in part, due to the limited sensitivity of tests that can be performed on-site.<sup>32</sup> The two most common diagnostic tests used



**Fig. 49.3:** Reciprocal effect of *T. vaginalis* and HIV. (a) Effect of trichomonas infection on HIV acquisition. (b) Effect of HIV status on risk of trichomonas infection. For women followed every 3 months for up to 3 years, Fig. 49.3 (a) shows the increase in risk over time of HIV acquisition for those women who have had a trichomonas infection (blue line) compared with those women who were never diagnosed with trichomonas (red line). Fig. 49.3 (b) shows the increase in risk of trichomonas infection following HIV acquisition (blue line) compared with those women who remained seronegative (red line) during the study period. More rapid decreases in the lines reflect rapid acquisition of disease. (Adapted from Napierella, et al. manuscript submitted.)

in clinical laboratory settings are wet mount microscopy and culture, and with such low sensitivities, these are poor diagnostic tools compared to DNA-based tests (see below).

Symptoms in men may include discharge, which may or may not contain significant quantities of lymphocytes or red blood cells, dysuria, pruritus, increased urinary frequency, or prostatitis. On rare occasions men may have urethral strictures or epididymitis. Symptoms generally appear within 7–10 days following exposure and it is possible that the infection may resolve spontaneously. Few longitudinal data are available to predict the frequency of such resolution. The vast majority of men with *T. vaginalis* may have no signs or symptoms of infection, thus confusing the measurement of natural clearance of disease. Diagnosis and treatment of these men remains clinically important in order to reduce the spread of the organism to sexual partners. Investigations performed more than 40 years ago reported infection in up to 45% of male partners of infected women and 100% of female partners of infected men.<sup>34</sup>

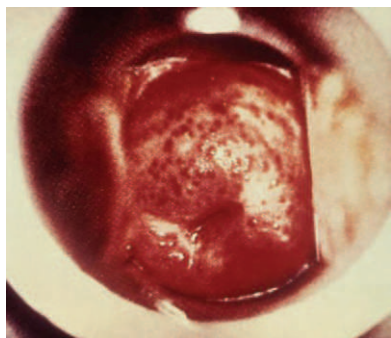
Asymptomatic carriers of trichomoniasis are an important reservoir of infection and diagnosis based solely on either the clinical signs or symptoms presented by the patient is unreliable.<sup>35</sup> Although *T. vaginalis* is commonly described in the context of non-gonococcal/non-chlamydial urethritis, trichomonas often occurs in men with chlamydia or gonorrhea. In one study, 23 of 37 men diagnosed with trichomoniasis and symptomatic urethritis had concomitant infection of gonorrhea.<sup>20</sup> Therefore, when screening for chlamydia and gonorrhea is appropriate, inclusion of screening for trichomonas should also be considered. With the development of nucleic acid-based diagnostics, this

testing can be performed on the urine samples being tested for chlamydia and gonorrhea.

Similar to men, women infected with *T. vaginalis* are also predominately without symptoms. While this has been well-documented over the last two decades, it is still common to encounter practitioners who believe that only symptomatic women should be tested. This misconception is supported by the fact that most testing is performed by wet preparation microscopy which is an insensitive test unless the number of organisms present is quite high. As a result, this test is most often positive in women with a high burden of organisms. High organism load leads to symptoms more often than a low burden. Thus the notion that all infected women have symptoms is a result of the poor sensitivity of the diagnostic test. Therefore, the utility of targeted diagnostics is questionable. When universal screening, rather than screening only symptomatic women, was evaluated in a women's correctional facility, the number of cases identified increased 4-fold.<sup>36</sup>

Women may experience vaginal discharge, vaginal itching, musty odor, dysuria, pelvic pain, irregular bleeding, and pain or bleeding on coitus. Clinical signs of infection in women include punctate bleeding of the cervix, often referred to as a "strawberry cervix" (Fig. 49.4), and a frothy discharge which is usually white but may be yellow or grayish in appearance. Vaginal pH greater than 4.5 may be noted in some women with trichomoniasis, but is not a highly reliable indicator.

In women, *T. vaginalis* infection has been linked to pelvic inflammatory disease (PID),<sup>37,38</sup> adverse outcomes of pregnancy,<sup>39–42</sup> and cervical cancer.<sup>16</sup> While the relationship between *T. vaginalis*



**Fig. 49.4:** Strawberry cervix. Typical appearance of the cervix of a woman infected with *T. vaginalis*. Punctate bleeding and micro abrasions are common features. Accessed from [http://bioweb.uwlax.edu/bio203/s2009/strous\\_mary/human\\_interaction.htm](http://bioweb.uwlax.edu/bio203/s2009/strous_mary/human_interaction.htm)

and PID in women with HIV has been shown to be strong (RR 1.9,  $p = 0.002$ ), in women without HIV the relationship was not significant ( $p = 0.4$ ).<sup>37</sup> The lack of a significant finding in HIV-negative women may have been due to a lack of power since the study sample included only 43 women. A study performed in the US did find an association between *T. vaginalis* and endometritis.<sup>38</sup> Additional studies using highly sensitive diagnostic techniques are needed to more clearly define the relationship between *T. vaginalis* and upper genital tract complications.

A prospective evaluation of the affect of *T. vaginalis* on pregnancy outcomes found significant associations between *T. vaginalis* and preterm delivery (before 37 weeks of gestation), low birth weight (infant weighing less than 2500 grams at birth).<sup>40</sup> Additionally, the likelihood of low birth weight was greater among Blacks (11%) than Hispanics (1.6%) or Whites (1.5%). These data emphasize the need for *T. vaginalis* control communities with high burden of disease and high likelihood of pregnancy complication.

## Diagnosis

### RAPID DIAGNOSTICS

*T. vaginalis* was first identified visually by microscopy of genital secretions by Donné in 1836.<sup>43</sup> Wet preparations, or wet mounts, are prepared by suspension of vaginal or urethral fluids in normal saline. The suspension is placed onto a slide and examined for motile trichomonads at 100 × magnification (low power) with confirmation of morphology using 400 × (high power). This technique remains the most frequently used diagnostic method even in technologically advanced settings. This test is simple, rapid, and inexpensive making it ideal for diagnosis in clinical settings. However, wet preparation microscopy is only 35–50% sensitive with higher sensitivity in women than men and in symptomatic individuals compared to asymptomatic patients.<sup>44,45</sup> This test is also hampered by rapid loss of motility at ambient temperatures and interference from other vaginal infections as mentioned above. However, despite the limitations of microscopy, this method was

found to be useful for identification of women with *T. vaginalis* in the context of HIV-control programs. In women attending family planning clinics in sub-Saharan Africa, a positive wet mount was associated with a nearly 4-fold increase in risk of HIV infection.<sup>22</sup> Therefore, microscopy, while not the best available diagnostic method, is preferable to no diagnostic evaluation in women at risk for HIV. In addition, microscopy offers the advantage of diagnosis during the office visit which increases the likelihood that patients will be treated for the infection.

Two commercially available assays with improved sensitivity can also be performed during an office visit. The OsomTrich (Genzyme Diagnostics, Cambridge, MA) dipstick assay provides results within 15 minutes and can detect twice as many infections as microscopy. The assay has excellent performance characteristics in low-<sup>46</sup> and high-prevalence populations.<sup>47</sup> An RNA probe assay, the Affirm (Becton Dickinson, Sparks, MD) test, can detect *T. vaginalis*, *Gardnerella vaginalis*, and *Candida* species in 45 minutes. This test performs better than microscopy and provides information that may lead to a diagnosis of yeast or BV as well as trichomoniasis, but requires specialized equipment and trained technicians.

### LABORATORY DIAGNOSTICS

Culture for detection of *T. vaginalis* was considered the gold standard of diagnosis until recently. Modified Diamonds Medium is enriched with yeast extract and supplemented with inactivated horse serum, amphotericin B, penicillin G, and gentamicin. This medium is formulated to allow trichomonads to grow, while suppressing bacterial growth. The addition of small amounts of agar reduces the oxygen tension, resulting in more prolific growth of trichomonads, which optimally grow and reproduce under anaerobic conditions.<sup>48</sup> Swabs containing vaginal secretions are inoculated into tubes containing medium and incubated for up to 5 days at 35–37°C. Each day a drop of the well-mixed culture fluid is placed on a slide and read microscopically in the same manner as a direct wet mount. Culture allows replication of the organisms thus increasing the probability of detection of motile organisms using microscopy. Culture will detect 1.5–3 times as many infections as direct wet mount microscopy in the clinic. An innovation in culture methodology is the InPouch culture system (BioMed Diagnostics, San Jose CA). This is a self-contained culture system that can be placed directly on to a microscope stage (Fig. 49.5). This allows microscopic evaluation of the entire culture rather than a single drop, thus improving the sensitivity.<sup>35,49,50</sup>

Currently, the most sensitive diagnostic methods for diagnosing trichomonal infections are nucleic acid amplification tests (NAATs).<sup>45,51–55</sup> These tests are based on enzymatic amplification of DNA or RNA to produce an exponential increase in the concentration of organism-specific targets. This amplification process increases the sensitivity of diagnostics to twice that of culture and 2.5–3.5 that of wet mount microscopy. NAATs are the most often used assays for screening for *C. trachomatis* and





**Fig. 49.5:** InPouch *T. vaginalis* culture system. Two culture pouches and the clip used to place these onto a microscope stage for direct examination of the entire culture. (Accessed from <http://www.biomeddiagnostics.com/images/InPouchTV.jpg>) In a longitudinal study of adolescent women,<sup>59</sup> 102 women provided vaginal swabs each week following diagnosis of trichomonas by NAAT. DNA-based testing was negative within 7 (95% CI 6, 9) days of treatment with metronidazole.

*N. gonorrhoeae*. Therefore, the opportunity to add trichomonas screening to samples collected for chlamydia and gonorrhea screening offers an advantage not previously available on a wide scale. While NAAT assays for *T. vaginalis* have been described that can be used in specialized research laboratories, fewer assays suitable for clinical labs were available.<sup>45</sup> Recently, a commercial assay has been made available for use on the Aptima system (Gen-Probe, San Diego, CA). While this assay is not FDA-approved at this time, it has excellent performance characteristics and is the only NAAT for detection of *T. vaginalis* RNA that is commercially manufactured.<sup>56</sup> Use of NAATs that can be performed on the samples collected for chlamydia and gonorrhea should encourage addition of trichomonas screening to routine sexual healthcare.

## Treatment

The recommended treatment for *T. vaginalis* infections is a single oral dose of 2 gram metronidazole (see review by Schwabke and Burgess).<sup>57</sup> Topical treatment has not been shown to be highly efficacious. The success rate of the oral regimen is approximately 85%. However, approximately 10% of failures are attributable to exposure to an untreated sexual partner. Therefore, management of sexual partners is strongly recommended. Metronidazole resistance has been reported in a small percentage of patients (<5%). Tinidazole, a compound related to metronidazole, is frequently used outside of the US to treat trichomoniasis (2 grams oral dose) with similar efficacy. This regimen may be useful for patients with metronidazole resistance infections. For a comprehensive review of clinical trials for treatment of trichomoniasis, see Forna and Gulmezoglu.<sup>58</sup> While treatment with these compounds is safe during pregnancy, there have been reports of a possible association between metronidazole treatment and preterm birth in women treated during the third trimester.<sup>57</sup>

Screening during the first trimester is recommended in order to minimize the possibility of adverse outcomes.

In a longitudinal study of adolescent women,<sup>59</sup> 102 women provided vaginal swabs each week following diagnosis of trichomonas by NAAT. DNA-based testing was negative within 7 (95% CI 6, 9) days of treatment with metronidazole. However, studies have shown high re-infection rates of trichomoniasis within a year following treatment, particularly in high-risk groups.<sup>13</sup> Therefore, women seeking care for symptoms more than 2 weeks after treatment should be evaluated for re-infection, particularly if their sexual partner(s) have not been treated. These data support the need for active partner management in any effort to control *T. vaginalis*, particularly in populations with high prevalence.

## Summary

- *T. vaginalis* is a sexually transmitted infection that is more prevalent than chlamydia and gonorrhea combined.
- Prevalence estimates are poor due to lack of public health monitoring of this pathogen.
- Women are 4–5 times as likely to be infected as men, but men carry and transmit the organism.
- Risks factors for trichomonas are similar to risks for other treatable STIs.
- *T. vaginalis* infection increases risk of acquiring HIV 2–4 fold and also increasing risk of transmitting HIV to sexual partners by increasing genital shedding of the virus.
- *T. vaginalis* infection has been implicated in increased risk of PID and cervical cancer and associated with preterm delivery.
- Infection with *T. vaginalis* is often asymptomatic and clinical algorithms designed to predict who should be tested are of limited utility.
- Diagnostic tests vary widely in sensitivity with wet mount performing worse than any other tests despite being the most commonly used method of detection. However, even the poorest test is preferable to not testing for *T. vaginalis*.
- NAAT diagnostics are the most sensitive assays available and can be bundled with chlamydia and gonorrhea screening with no additional effort on the part of the patient or clinician.
- Treatment with metronidazole is safe, inexpensive and efficacious particularly when coupled with treatment of infected sexual partners.

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# Intestinal Protozoa

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## Introduction

Intestinal protozoa have gained importance during recent years as a result of increasing world travel, economic globalization, and a growing number of chronically immunosuppressed people. Overall, contamination of water and food with fecal matter is the most common route of transmission of intestinal parasites. However, several intestinal parasites, including protozoa, are now also widely recognized as sexually transmitted infections (STIs), especially in the population of men who have sex with men (MSM). A summary of gastrointestinal syndromes associated with intestinal protozoa and other sexually transmitted infectious agents is provided in Table 50.1.<sup>1–3</sup>

## Epidemiology of Intestinal Protozoa Associated with Sexual Transmission

In the late 1960s through 1980s, in the pre-AIDS era, a substantial increase in enteric pathogens and associated intestinal disease emerged in communities of gay men in several cities across the

US and Europe. Sexual transmission of these enteric pathogens through oral-anal intercourse was first recognized in 1967, in a case series of MSM in New York City experiencing intestinal protozoan infections.<sup>4</sup> Later, several other studies of MSM populations confirmed the sexual transmissibility of intestinal protozoa.<sup>5–10</sup>

*Entamoeba histolytica*, an amoeba, and *Giardia lamblia*, a flagellate, are the pathogenic protozoa most commonly associated with sexual transmissibility.<sup>11–13</sup> The amoeba *Blastocystis hominis*<sup>14,15</sup> and flagellate *Dientamoeba fragilis*,<sup>16,17</sup> whose pathogenicities are controversial can also be sexually transmitted. In addition, the coccidia *Cryptosporidia*<sup>18–20</sup> and *Microsporidia*,<sup>21</sup> important causes of diarrhea in immunosuppressed persons, have been associated with sexual transmission. There are also some case reports of sexual transmission of *Isospora*, another significant intestinal pathogen in immunosuppressed populations.<sup>22</sup> However, direct sexual transmission of *Isospora* and *Cyclospora* is improbable. Oocysts of these coccidian are excreted unsporulated and need to mature outside the human host to become infectious.<sup>23</sup>

**Table 50.1:** Sexually Transmissible Gastrointestinal Syndromes, Intestinal Protozoan and Non-Protozoan Etiologies

Syndrome	Signs and Symptoms	Intestinal Protozoa	Other Etiologies
Enteritis	Large volume, watery diarrhea, mid-abdominal cramps, nausea with or without vomiting, malaise, weight loss	<i>Giardia duodenalis</i> <i>Cryptosporidium</i> spp. <i>Microsporidium</i> spp.	<i>Strongyloides stercoralis</i>
Proctocolitis	Small-volume diarrhea, lower-abdominal pain, abdominal tenderness, anorectal bleeding, sensation of incomplete defecation	<i>Entamoeba histolytica</i> * <i>Cryptosporidium</i> spp.	<i>Shigella</i> spp. <i>Salmonella</i> spp. <i>Campylobacter</i> spp. Cytomegalovirus†
Distal Proctitis	<i>Acute:</i> Mucopurulent anal discharge, anorectal bleeding, constipation, sensation of rectal fullness or incomplete defecation <i>Mild or Chronic:</i> Mucus streaking of stool, constipation, occasional feeling of incomplete defecation	Protozoa uncommon	<i>Neisseria gonorrhea</i> <i>Chlamydia trachomatis</i> Genotype A-K Genotype L (LGV) <i>Treponema pallidum</i> Herpes simplex virus

\*Also a cause of liver abscess.

†In HIV seropositive patients (CD4+ T-cell count <100).

Many of the intestinal protozoa associated with sexual transmission in high-risk populations are considered commensal and are not generally associated with gastrointestinal disease.<sup>6,7,24</sup> These include intestinal amoebas *Entamoeba dispar*, *Entamoeba coli*, *Entamoeba hartmanni*, *Endolimax nana*, and *Iodamoeba butschii*, as well as flagellates *Chilomastix mesnili*, *Trichomonas hominis*, and *Retortamonas hominis*.

Although heterosexual transmission of enteric protozoa can occur, the prevalence of intestinal protozoa is much higher in MSM. In more recent studies, prevalence of infection with at least one protozoa varies from 49% to 57% in MSM and from 13% to 16% in control heterosexual populations.<sup>15,25–27</sup> Colonization with multiple protozoa in the MSM population is also much more prevalent. In a recent study of Australian MSM, more than 40% of them had multiple protozoa on stool examination in comparison to less than 10% in the non-MSM control group.<sup>15</sup>

However, prevalence rates of specific intestinal protozoa are difficult to ascertain as most stool surveys are done in high-risk populations such as patients of STI clinics or in symptomatic

patients. In addition, stool studies are often done using one stool sample per participant, and therefore may underestimate the prevalence of intestinal protozoa.<sup>28</sup> Moreover, pathogenic *E. histolytica* is morphologically difficult to distinguish from nonpathogenic *E. dispar* and these are often reported as one category. The prevalence of common enteric protozoa in selected high- and lower-risk groups, as reported in some published studies, are shown in Table 50.2.<sup>6,15,24,25,27,29–35</sup>

Initially, the post-AIDS era, safer sex practices in reaction to the AIDS epidemic, led to a decrease in STIs including both symptomatic and asymptomatic enteric protozoan infections in MSM populations. However, the availability of highly active antiretroviral treatment (HAART) has led to a degree of sexual disinhibition associated with an increase in STIs in this population including intestinal protozoa in some populations.<sup>36</sup> Recently, pathogenic infections with *E. histolytica* re-emerged as potentially significant causes of intestinal disease in MSM and HIV-positive persons in the Australia and the Asia Pacific region including Japan, Taiwan, and the Republic of Korea.<sup>37–41</sup>

**Table 50.2:** Prevalence of Intestinal Protozoa in Selected High- and Low-Risk Study Populations

City	Year*	Population	N	Percent of population with stool samples positive for protozoal parasites†											
				Potentially Pathogenic					Nonpathogenic						
				<i>Entamoeba histolytica/dispar</i>	<i>Giardia intestinalis</i>	<i>Cryptosporidium parvum</i>	<i>Microsporidium spp.</i>	<i>Blastocystis hominis</i>	<i>Dientamoeba fragilis</i>	<i>Entamoeba coli</i>	<i>Entamoeba hartmanni</i>	<i>Endolimax nana</i>	<i>Iodamoeba butschii</i>	<i>Enteromonas hominis</i>	<i>Chilomastix mesnili</i>
Sydney	2007	MSM/HIV-	628	5	3	1	0	21	1	5	4	12	4	1	1
		MSM/HIV+	618	3	5	2	0	18	0	3	1	10	0	2	1
		Control	622	0	2	3	0	11	1	0	0	1	0	0	0
Sydney	1991	MSM/HIV+/-	128	37	3	0	0	76	2	38	15	40	19	1	2
Edinburgh‡	1999	MSM/HIV-	175	9	3	0	NR	26	NR	25	5	27	9	NR	NR
Edinburgh	1984	MSM	310	10	6	0	NR	NR	NR	10	1	5	2	NR	NR
London	1986	MSM	225	20	3	NR	NR	NR	4	20	14	24	4	NR	NR
		Control	129	0	2	NR	NR	NR	4	3	4	5	1	NR	NR
London	1984	MSM	83	12	8	NR	NR	NR	0	25	5	22	4	NR	NR
		Control	43	0	0	NR	NR	NR	0	5	0	2	0	NR	NR
San Francisco	1984	MSM	508	29	6	NR	NR	NR	1	21	25	38	13	NR	NR
San Francisco	1983	MSM	105	27	5	NR	NR	NR	1	17	25	38	18	NR	NR
		Control	415	1	2	NR	NR	NR	3	4	2	7	1	NR	NR
New York	1981	MSM	51	20	4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		Control	64	0	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
New York	1977	MSM	89	10	8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Adapted from Abdolrasouli A, et al. Sexual transmission of intestinal parasites in men who have sex with men. *Sex Health* 2009;6:185–94.

\*Year published.

†Rounded to nearest 1%.

‡Known HIV men excluded, 62% tested.

MSM indicates men who have sex with men.

As most of the protozoan infections in MSM are not associated with symptoms, many remain undiagnosed.<sup>6,7,24</sup> However, despite the high prevalence of asymptomatic infections, a better understanding among clinicians of sexually transmitted intestinal protozoan infections in this population is important. Even those with symptoms, often do not undergo proper evaluation for intestinal protozoa, especially in the absence of a travel history, as many clinicians are not aware of the risk of sexual transmission of intestinal parasites in this population. In addition, colonization with commensal protozoan organisms is often an indication of presence of other pathogenic protozoa in this population.<sup>8,31</sup> In the presence of symptoms, patients with a stool sample positive for commensal organisms should have evaluations of additional stool samples for pathogenic protozoa. Moreover, the higher prevalence of HIV in this risk group, in combination with the high underlying prevalence of protozoan infection, increases the risk of serious gastrointestinal infections in the immunosuppressed within this risk group.

## Sexual Risk Factors and Transmission

Oral-anal sex, also known as anilingus, is a sexual practice involving contact between the anus or perineum of one person and the mouth, lips, or tongue of another. Non-clinical, vernacular terms include rimming, rim-job, and salad tossing. It can be performed by people of all sexual orientations, and is a common practice in MSM.

Anilingus facilitates fecal-oral transmission of enteric pathogens and commensal organisms.<sup>10,42</sup> It is also the most significant independent risk factor associated with the transmission of *G. lamblia* and *E. histolytica* in the MSM population.<sup>6,7,31,34,43</sup> Frequency of anilingus and lack of anal cleaning before anal sex also have been correlated with protozoan infection.<sup>7,34</sup> Other risk factors for transmission of protozoa include number of sexual partners and history of other STIs, including syphilis and gonorrhea.<sup>34,44</sup> Some experts have argued that protozoan infections are less prevalent among heterosexuals because protozoan infection is not endemic in this group, and that there is less chance of exposure given generally fewer sexual partners and less frequent anilingus in this group.<sup>6</sup>

Among MSM, other than anilingus, other possible routes of sexual transmission of protozoan are oral-penile sex involving a fecally contaminated penis, intra-rectal transmission through the insertion of a contaminated penis into a rectum, digital-anal contact, fisting, and coprophagia.<sup>6,7,45</sup> Sharing sex toys and colonic cleansing equipment have also been implicated in transmission of protozoan infections.<sup>46</sup>

## Sexually Transmissible Protozoan Infections

Those intestinal protozoa excreted in the feces with the lowest infectious dose are most likely to be transmitted sexually. *E. histolytica* and *Giardia lamblia* both have a very low infectious dose (10–100 cysts) and are the most common and clinically significant sexually transmissible protozoan infections. *Cryptosporidium* also has a very low infectious dose (130 oocysts) and is sexually

transmissible. It is an important cause of intestinal disease and diarrhea in immunosuppressed persons, especially in MSM with advanced HIV infection. *Microsporidia* causes similar symptoms in immunosuppressed persons and can also be transmitted sexually, but is much less common, especially in the post-HAART era.

With the exception of *B. hominis* and *D. fragilis*, which have occasionally been associated with diarrheal disease in humans, other sexually transmitted protozoa are generally considered commensal and are not generally associated with intestinal disease in humans.

## ENTAMOEBA HISTOLYTICA

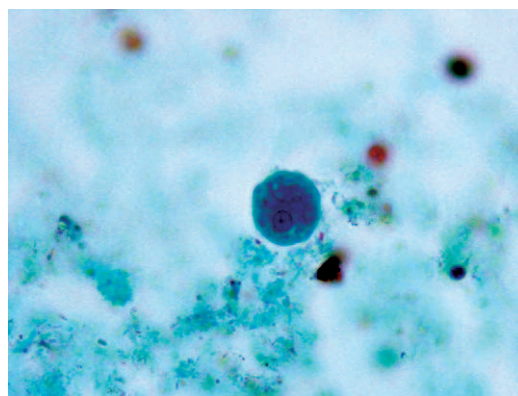
Amebiasis is an infection of the human gastrointestinal tract caused by *E. histolytica*. The parasite is capable of invading the intestinal mucosa and may spread to other organs, principally the liver, where it results in liver abscesses. *E. dispar* and *Entamoeba moshkovskii*, which are morphologically identical to *E. histolytica*, also colonize the human gut. *E. dispar* is now recognized as a species with no infective potential.<sup>47–50</sup> *E. moshkovskii*, was recently found to colonize 2% of MSM screened in a large study in Australia.<sup>15</sup> However, its role as a pathogenic organism is still being elucidated. In one study, *E. moshkovskii* was recognized as the only organism found in more than 5% of persons with diarrhea and abdominal pain.<sup>51</sup>

## Biology

*E. histolytica* exists in either trophozoite or cyst form.

### Trophozoite

The trophozoite is the motile form of *Entamoeba*. It is strongly affected by changes in temperature, pH, osmolarity, and redox potential. Actively motile amoebae are elongated, whereas resting trophozoites tend to be spherical (Fig. 50.1). The cell surface has



**Fig. 50.1:** *Entamoeba histolytica* trophozoite. Trophozoites vary in size from 12–60 microns. There is a single round nucleus, with a central dot or karyosome and an even distribution of chromatin around the nucleus. Ingested erythrocytes may be seen in the cytoplasm. (From Collection of Dr. John Keiser, George Washington University, 2009).



numerous openings that correspond to micropinocytic vesicles. The plasma membrane is covered by a uniform surface coat composed of glycoproteins. The cytoplasm of the trophozoite is characterized by the absence of mitochondria, golgi apparatus, rough endoplasmic reticulum, centrioles, and microtubules. The cytoplasm contains abundant vacuoles.<sup>52</sup>

### Cyst

*E. histolytica* cysts are round or oval hyaline bodies, surrounded by a retractile wall composed of fibrillar material. The plasma membrane has deep invaginations: polyribosomes and vacuoles containing dense fibrogranular material. Staining with iron hematoxylin makes the cytoplasm appear vacuolated with numerous glycogen deposits that decrease in size and number as the cyst matures. Iodine stains allow the clear visualization of one to four small nuclei.<sup>53</sup>

*E. histolytica*, *E. dispar*, and the more recently identified, *moshkovskii*, are morphologically identical. The existence of a species complex was first suggested in studies in which zymodemes (patterns of electrophoretic mobility of certain parasitic isoenzymes) were analyzed. Distinctive zymodemes were associated with symptomatic invasive disease or with asymptomatic carrier state. Further research with RNA and DNA probes clearly indicated two separate species: *E. histolytica* and *E. dispar*. Numerous antigenic differences between the two species have been demonstrated. Distinct epitopes present on the 170-kDa heavy subunit of the galactose inhibitable adherence lectin, which is a highly conserved antigen, are found in *E. histolytica* but not in *E. dispar*. Monoclonal antibody probes, and more recently, polymerase chain reaction (PCR), have been used to differentiate between the *Entamoeba*.

Morphologically, the presence of ingested erythrocytes is associated with the presence of *E. histolytica* and not of *E. dispar*, but these are often difficult to appreciate.<sup>54</sup>

### Life Cycle

Infection is acquired by ingestion of the cyst form that is resistant to the acidic pH of the stomach. Excystation occurs in the small bowel, with division of mature quadrinucleated cyst into four and then eight trophozoites by nuclear and cytoplasmic division. The trophozoites move into and colonize large bowel feeding on bacteria and cellular debris. If luminal conditions are less ideal, the trophozoites can encyst. The cysts are then excreted and may remain viable for weeks or months. Infection is not transmitted by trophozoites, which may be excreted during episodes of acute colitis, because of their rapid degeneration in environmental conditions. Infection may result from ingestion of cyst in contaminated food or water, or through oro-anogenital contact, as discussed above.

### Epidemiology

The main reservoirs of *E. histolytica* are humans. It is estimated that 10% of the world's population is infected by *E. dispar* or *E.*

*histolytica*. *E. dispar* infection is at least 10-fold more common than *E. histolytica* infection. Symptomatic invasive amebiasis develops only in 10% of individuals with *E. histolytica* infection. Therefore, disease will develop in only 1 of 100 individuals who are determined to be asymptomatically infected with *E. histolytica/dispar* by stool microscopy.

High rates of amoebic infection are seen in the Indian subcontinent, Southern and Western Africa, the Far East, and in South and Central America.<sup>55,56</sup> A high prevalence of *E. histolytica* was also shown in early studies of MSM (Table 50.2), but these studies did not differentiate between *E. dispar* and *E. histolytica* because of their morphologic similarity. Data from more recent studies indicates that most of these infections were likely due to *E. dispar*.<sup>15,25</sup>

Asymptomatic *E. histolytica* infection results in a humoral immune response and consequent production of serum antibodies, while *E. dispar* infection does not lead to a positive serology. There is a clear correlation between high seroprevalence and low socioeconomic and educational levels and inadequate housing conditions. Patients not at increased risk of infection but among whom the mortality due to invasive amebiasis is high include malnourished individuals, children younger than 1 year of age, pregnant women, and individuals receiving steroid therapy.

Recently, *E. histolytica* infection has also re-emerged as a significant cause of intestinal disease and liver abscess in MSM and persons with HIV in the Asia Pacific region.<sup>37,39,40,57,58</sup> It is unclear if HIV-related immunosuppression is associated with more serious infections with *E. histolytica*, as many previous studies have been contradictory and have had limitations. However, recent data suggest that HIV-infected persons may be at increased risk of invasive amebiasis.<sup>40,59</sup>

### Pathogenesis

The powerful lytic activity of *E. histolytica*, for which the parasite was named, has inspired a variety of approaches aimed at understanding the pathogenesis of invasive amebiasis. Intestinal invasive amebiasis can lead to amoebic ulcerative colitis, toxic megacolon, amoeboma or colonic granuloma, and amoebic appendicitis.

In invasive disease, intestinal ulcers may be found in the cecum, sigmoid colon, and rectum. These ulcers are characteristically shallow with broad elevated margins and are filled with fibrin.<sup>60</sup> The late invasive lesion presents with deep ulceration and a flask-like appearance.

This mucosal ulcer extends deep into a larger area of the submucosa, which seems to be particularly susceptible to the lytic action of the parasite. There is a rapid lysis of inflammatory cells around the invading amoebae, thus acute inflammatory cells are seldom found in biopsy samples or in scrapings of rectal mucosal lesions.

### Immunology

The time between infection with *E. histolytica* and appearance of local antibody responses remain unknown. High titers of antibodies tend to appear early in the disease and persist after

invasive or subclinical amebiasis is cured or controlled. The detection of antibodies depends on the sensitivity of the test used. If antibodies are measured by sensitive techniques of indirect hemagglutination test or by enzyme-linked immunosorbent assays (ELISA), they can be detected for more than 3 years after an invasive amoebic episode in the absence of recurrent infection.

Although a rapid humoral immune response is mounted by the host upon invasion by *E. histolytica*, the parasite has developed efficient evasion mechanisms that include resistance to complement and a mechanism for capping and shedding of surface antigens. It is therefore thought that humoral antibodies are not protective against *E. histolytica*. This conclusion is supported by the observation of a high rate of re-infection in persons with elevated antibody titers.

## Clinical Features

The term amebiasis includes all cases of human infection with *E. histolytica*. However, only a proportion of cyst-releasing individuals experience symptoms. Symptoms are caused by the penetration of the parasite into the tissues. This disease process is known as invasive amebiasis.

### Intestinal Amebiasis

Patients with acute amoebic colitis present with a 1- to 2-week history of abdominal pain, tenesmus, and frequent loose, watery stools containing blood and mucus. Despite the presence of mucosal ulcerations and occult blood in stools, fecal leukocytes may not be found because of the lytic activity of the parasite. Endoscopy may show the characteristic appearance of the punctate, hemorrhagic ulcers dispersed throughout a normal appearing mucosa.

Fulminant colitis is an unusual complication of amoebic dysentery and is associated with a grave prognosis. Patients with fulminant colitis present with severe bloody diarrhea, fever, and diffuse abdominal tenderness of rapid onset. The fulminant disease often progresses so rapidly that only 25% of adults with colonic perforation evident at laparotomy present with a rigid abdomen.

An amoeboma, or an amoebic granuloma, of the colon may present with a mass-like lesion in the right iliac fossa. Other less frequent complications of amoebic colitis include gastrointestinal hemorrhage, amoebic appendicitis, and amoebic strictures of the anus, rectum, or sigmoid colon.

### Extraintestinal Amebiasis

Amoebic liver abscess is the most common form of extraintestinal amebiasis. Patients typically present with fever and right upper-quadrant abdominal pain. Most patients have tender hepatomegaly. Jaundice is an unusual finding. Atypical features include shortness of breath and cough secondary to pleural effusion or rupture of the abscess into the pleural space. Less than 30% of patients have had active diarrhea at any time before presentation, even though

intestinal infection by *E. histolytica* must have occurred. Rupture of an amoebic liver abscess into the peritoneum occurs in 2% to 7% of cases; left-lobe abscesses are more likely to rupture because of their delayed clinical presentation. Brain abscess, and rarely, genitourinary disease, can also occur.<sup>61,62</sup>

## Diagnosis

Diagnosis of invasive intestinal amebiasis is traditionally made by demonstration of *E. histolytica* parasite in the stool. *E. histolytica* cysts may remain viable for some time in unpreserved stools, while trophozoites are labile and remain in stool for about 30 minutes. The diagnostic yield is better if the specimen is collected every day for a period of 3 days or longer. For examination of stool specimen, an iodine-stained smear as well as a concentration test should be done.

However, it is difficult to distinguish *E. histolytica* from *E. dispar* morphologically. Ingested red blood cells (hematophagous trophozoites) are indicative of *E. histolytica*, but this is an uncommon finding and can't be relied upon for diagnosis. Charcot-Leyden crystals are associated with amebiasis but are not specific for it. Confirmation with enzyme immunoassays or PCR is necessary.<sup>63</sup> PCR is more sensitive (80–100%) and more specific (85–100%) than microscopy, but is costly. Enzyme immunoassays are specific (100%) but are less sensitive than PCR.<sup>64</sup>

Serum antibodies to amoebae develop in response to *E. histolytica* infection but not to *E. dispar* infection. The absence of serum antibodies to *E. histolytica* after 1 week of symptoms is strong evidence against the diagnosis of invasive amebiasis of the colon or liver. Serum antibodies to amoebae are detected in 85% to 95% of all patients who present with invasive amebiasis or liver abscess. However, as antibodies persist for many years, ELISA or indirect hemagglutination cannot differentiate acute from remote infection in areas of high endemicity. Ultrasound is very useful for diagnosis of amoebic liver abscess. The classic appearance is of a nonhomogeneous hypoechoic round or oval mass with well-defined borders. Complete resolution of an amoebic liver abscess may take up to 2 years.<sup>65</sup> Percutaneous diagnostic needle aspiration is needed to differentiate between amoebic and pyogenic liver abscesses.

Newer diagnostic strategies involve detection of protein antigens in feces or serum by monoclonal antibodies and detection of parasitic DNA by use of nucleotide probes and PCR amplification. A commercial ELISA kit that uses monoclonal antibodies directed against an amoebic adherence lectin and accurately differentiates the true pathogen, *E. histolytica* from *E. dispar*, has recently been developed for clinical use.<sup>66,67</sup> Detection of amoebic lectin antigen in serum samples from patients with amoebic liver abscess is more than 95% sensitive if used prior to treatment with metronidazole.

## Management

Metronidazole 800 mg administered orally three times daily for 5–8 days is preferred treatment for invasive disease. Alternately, a single dose of Tinidazole 2 g can be used. Diloxanide furoate

500 mg three times daily for 10 days should be administered concurrently to decolonize the gut. Sexual partners within the preceding 3–4 months should be assessed for infection. Stool samples should be examined at monthly intervals for 3 months after treatment and should remain negative.<sup>1</sup>

## GIARDIASIS

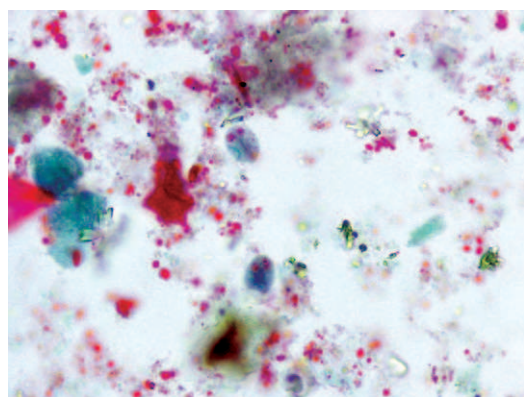
*G. lamblia* is an intestinal flagellate that infects both humans and animals, and is the most common cause of intestinal parasitic disease in humans worldwide. It is also known as *G. intestinalis* or *G. duodenalis*.

## Biology

*Giardia* possesses both trophozoite and cyst forms. The trophozoite is ‘sting ray’ shaped. The organism’s two nuclei and central parabasal bodies give it the appearance of a face with two bespectacled eyes and a crooked mouth (Fig. 50.2). There are four pairs of flagellae: anterior, lateral, ventral, and posterior. These parasites reside in the alkaline environment of duodenum and jejunum. They move about the unstirred mucous layer at the base of the microvilli with a tumbling or “falling leaf” motility. With the aid of a large ventral sucker, they attach themselves to the brush border of the intestinal epithelium. In the descending colon, the flagellae are retracted into the cytoplasmic sheaths and a cyst wall is secreted. These forms are oval in shape. The internal structures divide producing a quadrinucleate organism. The mature infective cyst forms can survive in extreme conditions.

## Epidemiology

Giardiasis has a cosmopolitan distribution. It has the highest prevalence in urban areas with poor sanitation. In developing countries, infection rates may reach 25% to 30%. But even in



**Fig. 50.2:** *Giardia lamblia* trophozoite. Trophozoites are 9–12 microns long and 5–15 microns wide. They are characterized by 2 nuclei with large central karyosomes, two parabasal bodies below the nuclei, a large ventral sucking disk for intestinal attachment, and the presence of flagella. (From Collection of Dr. John Keiser, George Washington University, 2009).

developed countries, it is the most frequently identified intestinal parasite. Young children and young adults are most frequently infected. Children with luminal immunoglobulin A deficiencies are most susceptible to *Giardia* infection.

Infection usually follows ingestion of viable cysts of the parasite in contaminated food or water. Fecal-oral transmission of *Giardia* among MSM is also well documented and prevalence rates in this population vary from 2% to 13% in most studies (Table 50.2). Disease in this population is associated with 50% of infected cases. *Giardia* has been associated with HIV, and in some studies has been linked with more severe disease in this population.

## Life Cycle

As few as 10–25 cysts may establish infection. Excystation is initiated by contact with acidic gastric juice followed by release of one or two trophozoites. The trophozoite (Fig. 50.2) infects the duodenum and upper intestine and gives rise to clinical sequelae. As trophozoites pass through the small intestine to the colon, encystation occurs.<sup>68,69</sup>

## Pathogenesis

The sequence of pathogenic events is ingestion, then colonization followed by adhesion. The mechanisms of parasite adherence include (i) mechanical adhesion related to ventral flagella and ventral sucker disc, and (ii) lectin-mediated, mannose-dependent adhesion.

Giardiasis produces absorptive defects associated with parasite-induced damage at the microvillous border. The microvillous damage is usually proportional to the parasite density. Parasite movement on the surface of small intestine may lead to interruption of lectin adhesion to the enterocytes, disordering of enzymes and surface membranes of microvilli, and the accumulation of osmotically active particles of unabsorbed nutrients in the lumen leading to diarrhea. Active uptake of bile salt concentrations by trophozoites also alters micelle formation causing malabsorption of fats. In addition, *Giardia* can interfere with the function of pancreatic lipase *in vitro*, and small bowel bacterial overgrowth can occur.<sup>70–73</sup>

## Pathology

Morphological changes can occur in the jejunum and the duodenum and are associated with more severe disease. Villi are often shortened and crypts are elongated. Intraepithelial lymphocytes are increased in number. Lamina propria infiltrate with plasma cells and lymphocytes may also be seen. *Giardia* trophozoites may be visualized in the intervillous spaces and on the microvillous border of the epithelial cells.

## Clinical Features

The majority of individuals infected with *Giardia* are asymptomatic. Typical clinical symptoms begin 1 to 3 weeks after ingestion of cysts and are marked by diarrhea, malaise,



flatulence, greasy stools, and abdominal cramps. Diarrhea is often explosive in nature and is foul smelling. Vomiting and fever are less common and blood- or mucus-tinged feces are rare. Individuals can also develop subacute and chronic infections. In patients with chronic giardiasis, diarrhea can lead to dehydration and malabsorption. Children may develop growth retardation. Healthy patients with domestically acquired giardiasis from sexual or other close personal contact commonly present with gas and cramps but no frank diarrhea.

## Diagnosis

Laboratory diagnosis of *Giardia* infection is made by examination of fresh stool samples for cysts and trophozoites. At least three stool samples should be examined before a negative result is reported.

If stool tests are negative, jejunal biopsy can be helpful in making a diagnosis. In addition, many commercial antigen tests are available. These tests are more sensitive (90–100%) than microscopy. PCR can also be used to diagnose *Giardia*.<sup>74,75</sup>

## Management

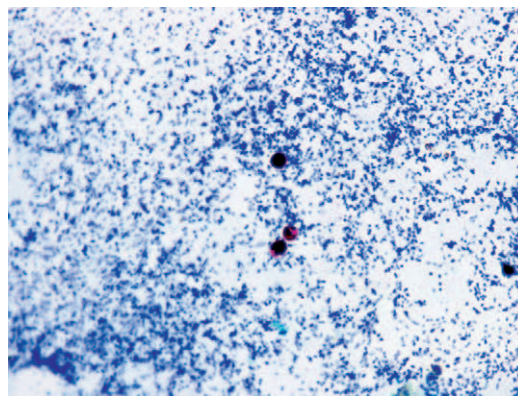
Preferred therapy for *Giardia* includes metronidazole 2 g orally as a single dose daily for 3 days or metronidazole 400 mg orally three times per day for 5 days. Alternately, Tinidazole 2 g orally as a single dose may be used. All sexual partners within the preceding month should be assessed for symptomatic infection. Three negative consecutive stool samples taken at least 24 hours apart should be evaluated to confirm cure.<sup>1,76–79</sup>

## CRYPTOSPORIDIOSIS

The *Cryptosporidium* species are intracellular protozoan parasites that have emerged as an important cause of diarrhea among humans. Of the 10 species of *Cryptosporidium*, only *C. parvum* is widespread in humans and other mammals. This parasite has received a great deal of attention in the past several years because of the persistent and profuse diarrhea and morbidity it causes in immunocompromised patients, most notably in those with the acquired immunodeficiency syndrome (AIDS). It is also associated with community water-borne outbreaks of diarrhea in otherwise healthy individuals.<sup>80,81</sup>

## Life Cycle

*C. parvum* is an *apicomplexan* protozoal parasite. *Cryptosporidium* exists in the environment as a 5- $\mu$ m oocyst (Fig. 50.3), which contains four sporozoites. Humans and animals are infected by ingesting these oocysts, which travel through the gut lumen to the small intestine where they rupture, releasing the sporozoites. Sporozoites are infective and attach to epithelial cells, after which they become enveloped by the host apical cell membrane and differentiate into the spherical trophozoites. *C. parvum* resides intracellularly but outside of



**Fig. 50.3:** Acid-fast *Cryptosporidium* oocysts, usually approximately 5–7  $\mu$ m in diameter. (From collection of Dr. John Keiser, George Washington University, 2009).

the cytoplasm, in contrast to the other intracellular pathogens (e.g., *Toxoplasma*) that are located in parasitophorous vacuoles within the cytoplasm.

## Immunology

The mechanism by which *Cryptosporidium*-infected intestinal epithelial cells initiate immune response is not entirely clear. One apparent mechanism in human cells involves the production of tumor necrosis factor alpha, interleukin-8, and C-X-C chemokines by infected mucosa.<sup>82,83</sup>

## Epidemiology

Human infection with *Cryptosporidium* has been reported in more than 90 countries and 6 continents. Specific groups at greater risk of infection include children, malnourished persons, and immunocompromised individuals including AIDS patients, transplant recipients, and persons receiving chemotherapy.

The oocyst is the form transmitted from an infected host to a susceptible host by the fecal-oral route. Routes of transmission can be (i) person to person, (ii) animal to animal, (iii) animal to human, (iv) water-borne, (v) food-borne, and (vi) possibly air-borne.<sup>84–89</sup> Oocysts of *C. parvum* can remain viable for many months. *Cryptosporidium* has been recognized as the most common parasite associated with chronic diarrhea among MSM with HIV-related immunodeficiency and is associated with a prevalence of up to 33% in some HIV-positive MSM populations in the pre-HAART era.<sup>90</sup>

## Pathogenesis

Both the processes of intestinal absorption and secretion are regulated by intestinal epithelial cells infected by *Cryptosporidium*. In experimental models of cryptosporidiosis, impaired glucose-stimulated sodium and water absorption and/or increased chloride secretion have been identified as pathogenic mechanisms. Abnormalities in the barrier

properties of the intestinal epithelium, mediated in part by intercellular junctional complexes also contribute to *Cryptosporidium* diarrhea. In addition, investigations have found evidence of permeability defects and decreased resistance across *C. parvum*-infected intestinal cell lines.

## Clinical Features

Although asymptomatic infection is well documented, more than half of infected persons develop chronic disease and about 10% develop fulminant disease. The incubation period of *Cryptosporidium* infection ranges from 2 to 14 days. The manifestations include watery and profuse diarrhea with abdominal cramps, nausea, vomiting, and low-grade fever. In immunocompetent individuals, the disease is usually self limited.

In contrast, the duration of illness is prolonged in the immunocompromised host and the symptoms are generally more severe. In addition to diarrhea, malabsorption can result secondary to decreased absorptive surface. This contributes to the wasting syndrome seen in HIV-infected persons with advanced immunosuppression. Immunocompromised patients who develop biliary infection can also present with acute cholangitis.

*Cryptosporidium* infection can also lead to chronic malnutrition in previously normal children. This may be due to persistent malabsorption secondary to *C. parvum*-induced intestinal injury or enhanced susceptibility to other pathogens.<sup>91</sup>

## Diagnosis

A variety of diagnostic options are available for the detection of *Cryptosporidium* in stool samples. The diagnosis depends on the identification of the 5- $\mu$ m spherical oocysts in stool or the intracellular stages within biopsy specimens of gastrointestinal mucosa. Duodenum is a reasonable site for biopsy in AIDS patients infected with cryptosporidiosis.<sup>92</sup>

Conventional detection methods include stool concentration and staining of fecal smears. Auramine-rhodamine screening of stool sediment smears followed by acid-fast (Ziehl-Neelsen) staining is a sensitive and specific approach for the diagnosis. Cryptosporidial oocysts should be discriminated from *Cyclospora* oocysts which are significantly larger (10  $\mu$ m).

Immunological-based techniques including polyclonal fluorescent antibody tests, latex agglutination reactions, immunofluorescence with monoclonal antibodies, ELISA, and solid-phase qualitative immunochromatographic assays have been developed for the detection of cryptosporidiosis.<sup>93,94</sup> These tests may also show some cross-reactivity to non-*C. parvum* oocysts.

A variety of PCR tests offer alternatives to conventional diagnosis of *C. parvum* for both clinical and environmental specimens. Although PCR is rapid, highly sensitive, and accurate, it has several limitations. False-positives can result from detection of naked nucleic acids, nonviable microorganisms, and laboratory contamination. The PCR can also be inhibited by some stool components. An advantage of PCR is that genetic information obtained from the sample may permit nonhuman pathogens to be distinguished from human pathogens.<sup>95–98</sup>

## Summary

Common Sexually Transmitted Protozoa, Major Clinical Syndromes, Diagnosis and Management

Organism	Major Clinical Presentation	Diagnosis	Management
<i>Entamoeba histolytica</i>	Amebiasis Intestinal proctocolitis Liver abscess	Stool for ova and parasites, serology, fecal antigen testing, Ultrasound, serologic tests	<i>Treatment</i> Metronidazole or tinidazole plus diloxanide furoate to decolonize the gut <i>Follow-up stool samples</i> Should be examined at monthly intervals for 3 months after treatment <i>Testing of Partners</i> Partners within the proceeding 3–4 months should be assessed for infection
<i>Giardia lamblia</i> (intestinalis)	Malabsorption and noninflammatory diarrhea	Stool for ova and parasites, fecal antigen testing	<i>Treatment</i> Metronidazole or Tinidazole <i>Follow up stool samples</i> Three consecutive stool samples 24 hours apart to confirm cure <i>Testing of Partners</i> Partners within preceding month should be evaluated
<i>Cryptosporidium parvum</i>	Noninflammatory diarrhea, usually self-limiting Severe diarrhea and cholangitis in HIV-related immunosuppression	Acid-fast staining of stool samples, small bowel biopsy	<i>Treatment</i> Immune reconstitution, supportive care, nitazoxanide <i>Follow-up stool samples</i> Not necessary in immunocompetent patients <i>Testing of partners</i> Not recommended under current guidelines

## Management

Unfortunately, there is no completely effective treatment for *Cryptosporidium*. Cellular immunity is critical in clearing the pathogen. In immunocompromised hosts, cryptosporidiosis can be life-threatening, particularly if CD4<sup>+</sup> cell count is below 200/ $\mu$ L. In this case, ideal treatment involves restoring of immune function with HAART.<sup>99</sup> Another agent that may have some benefit in severe infections is nitazoxanide taken 500 mg twice daily. Recommended duration of therapy is 3 days for immunocompetent persons and 14 days for those with HIV-related immunosuppression.<sup>100–102</sup>

In immunocompetent patients, infection is self-limited with duration of 2–26 days. Treatment consists of adequate hydration with or without antimotility agents to control symptoms. Sexual partner notification and assessment is not recommended in the current guidelines. Follow-up stool samples in immunocompetent patients are not necessary.

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## Scabies

Human scabies is an ectoparasitic infestation caused by the itch mite *Sarcoptes scabiei* var *hominis*. It is the first human disease for which an infectious agent was identified as the cause.<sup>1</sup> The disease has assumed pandemic proportions and in the present scenario of human immunodeficiency virus (HIV) infection, scabies has become more rampant with atypical presentations.

Although scabies is frequently described as a sexually transmitted infection, opinions differ on the appropriateness of this description. Some authors reported sexual transmission in 60–80% of patients with scabies. In 1946, Heilesen reported sexual transmission in 62% of the 231 patients he had treated.<sup>2</sup> Felman et al.<sup>3</sup> suggested that sexual transmission is the primary mode of spread in adults and reported that 60–80% of cases of scabies were acquired by sexual contact or sleeping together in the same bed. In studies in the United States Navy, most cases were believed to be acquired by sexual contact.<sup>4</sup> Some authors suggested that the increase in scabies in the 1970s was due partly to increased promiscuity and that it ran parallel to the increase in incidence of head and pubic lice.<sup>4,5</sup>

In contrast to these views, it has been stressed that transmission of the mites requires close body contact but not necessarily sexual contact, unlike sexually transmitted infections such as syphilis. Further, scabies does not fit in the classic patterns of a sexually transmitted infection. Trends in the incidence of scabies do not parallel those of common sexually transmitted infections. Gordon et al.<sup>6</sup> suggested that it should more appropriately be called a “family disease.”

It is true that scabies, as a sexually transmitted infection, has not been widely studied but venereologists often attach significance to this condition, as it could be an indicator to look for the presence of other sexually transmitted infections. Whatever be the mode of transmission, the clinical presentation of scabies does not vary much. Scabies has been a common disease for at least 3000 years. The word scabies is believed to be derived from the Latin term *Scabere*, meaning “to scratch” and possibly from the “scabs” of secondary bacterial infection.<sup>7</sup> The disease is

known by various names like acariasis, 7-year itch, camp itch, and Norwegian itch. In mammals, the condition is known as sarcoptic mange, and in birds as scaly leg. The itch mite was known for centuries before it was accepted by the medical world as the causative agent of scabies. Avenzoar and his student Averroes in Spain first described the scabies mite in the 12th century, although they did not link it with the associated skin eruption.<sup>1</sup> August Hauptmann is believed to be the first person to show the mite in 1654. Giovanni Bonomo, in a letter to Fransesco Redi, described and drew the scabies mite in 1687.<sup>8</sup> von Hebra showed in 1844 that scabies was a local and not an internal disease. Thomas Hillier in 1865 wrote in his “Textbook of Skin Diseases” that the mite *Sarcoptes hominis* was the cause of scabies. It has thus been described as the first disease in humans with a known cause.<sup>1</sup> In 1943, Mellanby described the life cycle of the mite.

## BIOLOGY

The *Sarcoptes scabiei* belongs to the phylum Arthropoda, class Arachnida, order Acariformes, suborder Astigmata and family Sarcoptidae.<sup>9</sup> Mites of dogs, horses, and other animals are morphologically indistinguishable from *S. scabiei* var *hominis*, but are physiologically different and host specific.

## MORPHOLOGY

The adult female mite is ovoid in shape with a translucent white color, 330–450  $\mu\text{m}$  long and 250–350  $\mu\text{m}$  wide (Fig. 51.1). There are four pairs of legs. The anterior two pairs end in suckers and the posterior two pairs end in bristles (Fig. 51.2). The adult male mite is roughly half the size of the female. The main difference is the presence of sucker on the fourth leg (Fig. 51.3), which is a bristle in the female.<sup>10</sup>

## LIFE CYCLE

The female, once impregnated, is fertile for the rest of its life. Ovigerous female is the most important infective form. A single fertilized female can initiate and perpetuate the infection. It selects



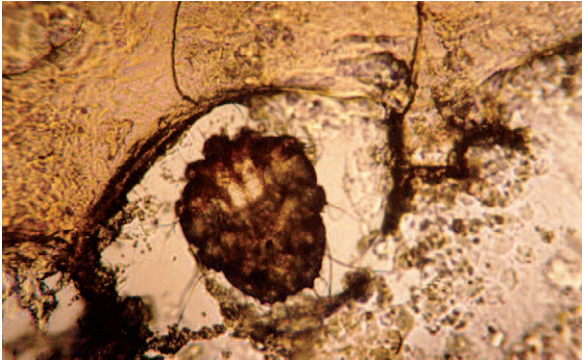


Fig. 51.1: Adult female mite.

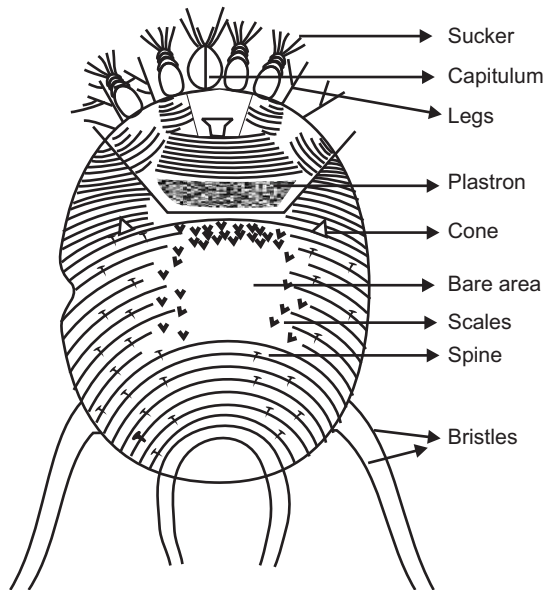


Fig. 51.2: Dorsal surface of adult female.

places on the body where the skin is thin and wrinkled. The mite walks on the surface of the skin at a speed of about 2.5 cm/min. Burrows are created at the base of the stratum corneum of the epidermis at a rate of 2–3 mm/day, which are seen as thin twisting lines. The burrowing time is about 8 hours, mainly in the night. It feeds on liquid oozing from the cells it has chewed. It lays eggs in groups of 2–4/day and the total number of eggs laid is about 40–50.<sup>10</sup> The life cycle of *S. scabiei* is depicted in Fig. 51.4.

### SURVIVAL

The female mite survives away from the host for a maximum of 2–4 days at room temperature. The mites cannot use water vapor from air and must obtain water from the host. So fomites may not play a major role in the transmission of scabies.<sup>11</sup>

### EPIDEMIOLOGY

The incidence of scabies varies from time to time. The view that major scabies epidemics occur in 30-year cycles and last about 15 years is based largely on data from the 20th century, in which

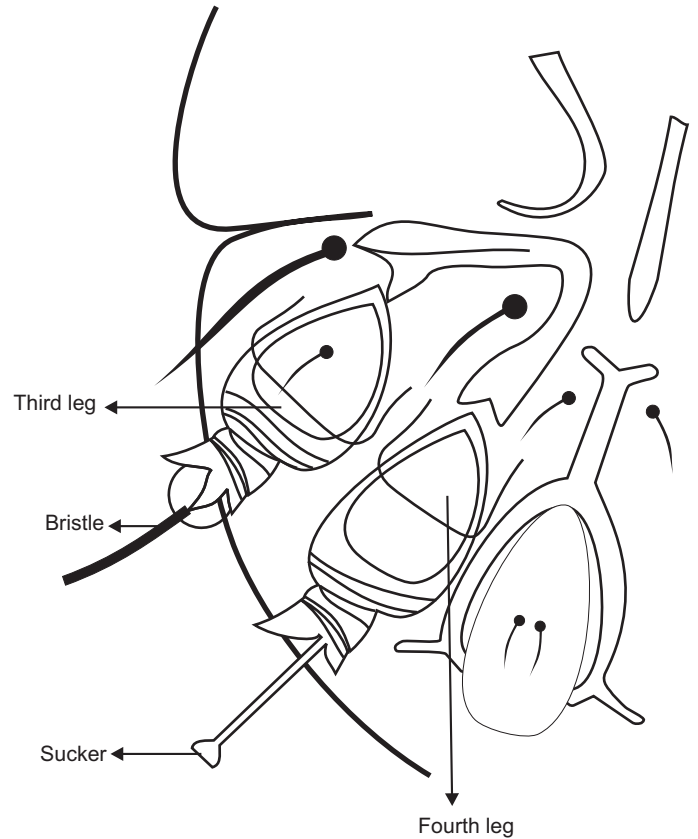


Fig. 51.3: Terminal parts of ventral surface of adult male.

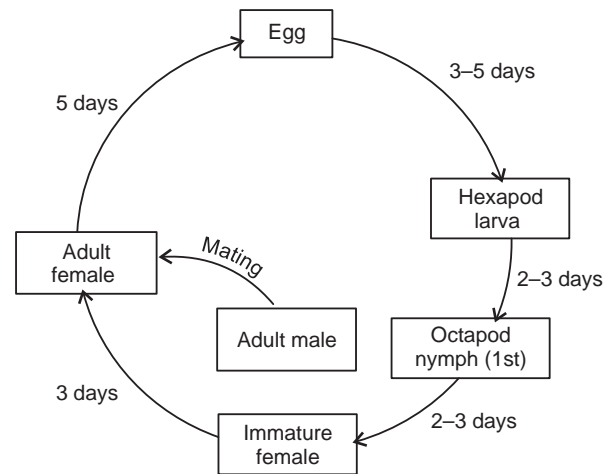


Fig. 51.4: Life cycle of *Sarcoptes scabiei*.

there had been three pandemics. Variations in herd immunity were postulated as the cause. Many authors have refuted this hypothesis. They argue that natural calamities, world wars, major economic depressions, and population movement were the major factors leading to the two pandemics which peaked in 1918 and mid 1945. Thus the frequently quoted 30 years cyclic period may be an oversimplification of the epidemiology of the disease.<sup>8</sup>

Scabies is a disease of the clean and the dirty, though the clinical profile may be different. Good personal hygiene serves little protection as shown in nosocomial outbreaks.<sup>12,13</sup>

Close physical contact, as in sharing a bed or sleeping crowded together, is the main mode of transmission. About 15–20 minutes of close physical contact is adequate for transmitting the disease. Fomites do not play a significant role in the transmission of scabies but reasonable precaution has to be taken in case of crusted scabies.<sup>8,11</sup> Though fertilized female mites are often implicated for transmission, there are far greater numbers of immature mites on the skin surface, which would appear more likely to be involved.<sup>6,8</sup> An infested person, during the incubation period is an important source of infection.

Scabies has been classified as a sexually transmissible disease, but the close physical contact, rather than the sexual act, could be responsible for the disease transmission.<sup>8</sup> In a study in Sheffield, England, “family contact” was focused as a major factor in the spread of scabies. The secondary attack rate within the family was 38%. The frequent sources for introduction of scabies into the home were friends and relatives (90%).<sup>14</sup>

In developing countries about 81% of scabies is seen in children below 14 years of age.<sup>12</sup> The rampant variety of scabies associated with HIV infection and other immunosuppressive states has resulted in hospital epidemics.<sup>8</sup>

## IMMUNOLOGY

The immune response to scabies mite is not absolute, but plays a major role in the epidemiologic studies and in the development of the clinical manifestations of scabies. Delayed hypersensitivity response plays a crucial role in eliminating the disease.<sup>15</sup> Some mite proteins have immunomodulating properties that facilitate host invasion by down regulating the inflammatory response of Langerhans and dendritic cells in the skin and possibly inhibiting a delayed immune reaction. Ordinary scabies induces a T-cell infiltrative response to the mite with a CD4+/CD8+ ratio of 4/1. Immunohistologic studies in crusted scabies reveal a predominantly CD8 + T-cell response. It is hypothesized that the activated CD8+ cells induce a dysregulated keratinocyte apoptosis and thus contribute to progressive epidermal hyperproliferation. The clinical appearance of crusted scabies is similar to that of psoriasis and suggests that the overexpression of Th1 cytokines may play a driving force in the dermatopathology.<sup>16</sup>

In primary infestation, the symptoms appear slowly after a lapse of about 4–5 weeks. The mite population is greatest during this incubation period. Once symptomatic, the mite population reduces dramatically. This is due to the mechanical removal of the mite by scratching and the immunological response by the host. Symptoms appear earlier (within 24–48 hours) in reinfestation. The rash is much more extensive and is not limited to the sites of infestation. Immunosuppressed patients appear particularly susceptible to severe forms of scabies. A high frequency of HLA A11 has been observed in scabies. Humoral immune response is also seen,<sup>15,17</sup> but its significance is not known. Crusted scabies is

associated with extremely high mite burden, elevated antibody levels, and eosinophilia.<sup>18,19</sup> The development of immunity neither ensures elimination nor does it confer immunity against reinfestation. Though the number of mites reduces, spontaneous cure, without treatment is not achieved.<sup>8</sup>

## CLINICAL FEATURES

### Classical Scabies

The diagnosis of scabies is essentially clinical. The primary lesions are burrows, papules, vesicles, bullae, and nodules. Burrows are the pathognomonic lesions and are 5–15 mm long linear eruptions. Erythematous papules are more common than burrows. They are more extensively distributed than mite bearing skin surface.<sup>20</sup> These lesions are referred to as “scabid.”

The lesions are distributed over the webs of the fingers, flexor medial aspect of the wrist, elbow, anterior axillary fold, nipple and areola in females, and genitalia in males. Lesions are bilaterally symmetrical. An imaginary circle, intersecting these main sites is called the “circle of Hebra.” The periumbilical region and lower portion of buttocks are also common sites of involvement. In infants and children, scalp, face, palms, and soles are also involved, which are characteristically spared in adults due to a high concentration of pilosebaceous follicles on the face and thick stratum corneum in palms and soles. Itching, usually generalized, is a predominant symptom and a nocturnal aggravation of pruritus is characteristic.

In adult males, scabietic lesions are sometimes seen only over the genitalia (Fig. 51.5a & b). These may indicate sexual transmission. They are raised, slightly elongated nodular lesions with the burrow tracks each seen as a thin, black, irregular line. Mechanical scratching by the patients removes the roof of the burrow leaving a shallow longitudinal ulcer. The lesions are commonly seen on the preputial skin, shaft of penis, scrotum, and glans penis.<sup>21</sup>

### Crusted Scabies

Crusted scabies (CS) was first described in Norway lepers by Danielssen and Boeck in 1842. Crusted scabies is remarkably asymptomatic in most of the cases in spite of the presence of more than two million organisms on the host, pointing towards the impaired immunological function.<sup>15</sup> It is characterized by marked crusting and scaly plaques, sometimes resembling psoriasis, in the usual scabietic sites. In addition, the palms, soles, head and neck, and lumbosacral areas may be involved. The helix of the ear is a constant site of involvement. CS may also present as erythroderma. Generalized lymphadenopathy may be present. Nails are dystrophic and discolored and masses of horny debris may accumulate under the nails.

Whenever CS is diagnosed, it is very important to find out the underlying associated conditions, like Down’s syndrome, Turner’s syndrome, neurological disorders with poor cutaneous sensation like Hansen’s disease or tabes dorsalis, and immunosuppression due



\*c+



\*d+

**Fig. 51.5:** (a) Scabietic lesions over the male genitalia; (b) Scabietic papules on prepuce.

to various causes, the most important of which is HIV infection.<sup>22–24</sup> Involvement of characteristic sites and occurrence of classical scabies in family contacts give a clue to the diagnosis.<sup>25</sup>

### Nodular Scabies

Nodular scabies is more common in young adult males. The persistent scabietic nodules present as reddish brown, extremely pruritic, excoriated nodules, 5–15 mm in size (Fig. 51.5b). Male genitalia and axillae are the common sites of involvement. Buttocks, anterior abdomen, and thighs are sometimes involved. It is associated with lesions of classical scabies in approximately two-third of patients. Patients with longer duration of untreated or inadequately treated scabies are more likely to develop nodular lesions. Lesions may persist despite antiscabietic therapy. In chronic cases, intralesional steroids are useful.<sup>26</sup>

### Scabies in Babies/Neonatal Scabies

The distinct features of neonatal scabies are the involvement of the face, neck, scalp, palms, and soles, in addition to the classical sites, tendency to form vesicles and pustules early in the course of the infestation, lack of pathognomonic burrows, presence of secondary eczematous changes, poor feeding, and failure to thrive. Examination of close contacts, especially the mother, may give a clue to the diagnosis.<sup>27,28</sup>

### Animal-Transmitted Scabies

Scabies affecting animals like dogs, cats, and pigs is called “sarcoptic mange.” Animal mites, though host specific, may accidentally be transmitted to humans, but cannot complete their life cycle. Animal scabies is found in occupations typified by names such as “dairyman’s itch,”<sup>8</sup> “cavalryman’s itch,” and “Buffaloman’s itch.”<sup>8</sup> Scabies contracted from dogs has been described as “pseudoscabies.”

It has a shorter incubation period of 1–10 days. It is common in children and seen at sites of contact with the animal, e.g., flexor forearm, lower part of chest and abdomen. Burrows are usually absent. The course is self-limited once the contact with the animal is avoided, although good results have been achieved with treatment. There is no need to treat the contacts.<sup>29</sup>

### Scabies Incognito

Scabies treated with topical or systemic steroids presents with an unusual clinical manifestation with bizarre crusted lesions involving atypical sites. The itching is less, but the mite population is more.

### Scabies in Clean

Lesions are few and are commonly seen on the genitalia and thighs. Other classical sites are usually spared. Papules are seen but burrows are uncommon. They may present as nodular lesions or chronic urticaria.<sup>26</sup>

### Scabies in Bedridden

Bedridden patients may have scabies limited to the sites of constant contact with the sheets.<sup>8</sup>

### Scabies Galeuse/Chancre Galeuse

Rarely, an individual with scabies may acquire syphilis. As a result, a syphilitic chancre can occasionally occur in a cutaneous lesion of scabies.<sup>26</sup> The initial lesion of scabies may be the route of entry for *Treponema pallidum*.<sup>21</sup>

### COMPLICATIONS

The common complications of scabies and its sequelae are secondary bacterial infection, glomerulonephritis (immune complex mediated), post-scabietic pruritus, and persistent delusions of parasitosis.<sup>20</sup> Secondary bacterial infections in genital region may result into inguinal lymphadenopathy, and





**Fig. 51.6:** Inguinal lymphadenopathy due to secondarily infected scabies.

sometimes, bubo formation (Fig. 51.6). Septicemia, bacterial endocarditis, and death have been reported in association with scabies, especially in immunocompromised hosts.<sup>30</sup>

## DIAGNOSIS

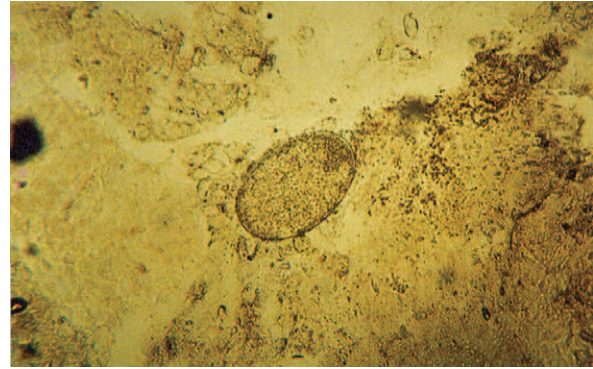
Diagnosis of scabies is essentially clinical. The classical diagnostic features are the demonstration of burrows, distribution of lesions at the characteristic sites, nocturnal aggravation of pruritus, a family history of scabies and demonstration of the mite, ova, immature stages, or the scybala (fecal matter).<sup>20</sup>

Laboratory techniques for the identification of burrows include mineral oil application to the skin surface, tetracycline fluorescence test, and the Burrow-ink test. The definitive diagnosis of scabies is by the demonstration of the mite or its products under microscopy (Figs. 51.1 and 51.7a&b). Scrapings are examined under low power (10×) after addition of a few drops of 10% potassium hydroxide solution.

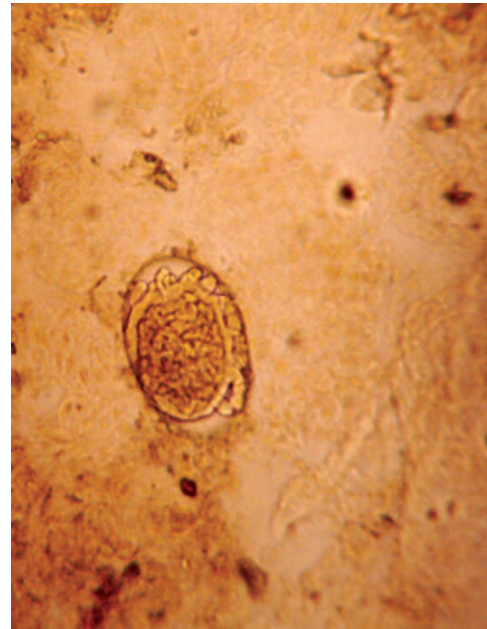
Epiluminescence microscopy has been used to demonstrate the mite and the burrow. Electron microscopic and scanning electron microscopic features are also described, but are not useful in routine clinical practice. In the future nested PCR may prove to be a useful tool for diagnosing scabies in those in whom disease is clinically suspected but mites had not been detected.<sup>31</sup>

## DIFFERENTIAL DIAGNOSIS

John Stokes states that scabies is both the easiest and yet the most difficult diagnosis in dermatology.<sup>26</sup> Scabies has to be differentiated from the following diseases: (i) papular urticaria or insect bite reaction, in which the lesions are mainly distributed on the exposed areas; (ii) dermatitis herpetiformis, the classical distribution of lesions on the upper back and lumbosacral areas, and grouping of lesions help differentiate it from scabies; (iii) contact dermatitis, history and presence of classical features of scabies help rule out contact dermatitis; and (iv) atopic dermatitis is at times difficult to differentiate from scabies in children, as it presents as acute eczema. A positive history of atopy, absence



\*c+



\*d+

**Fig. 51.7:** (a) Immature eggs of *Sarcoptes scabiei*; (b) Mature eggs of *Sarcoptes scabiei*.

of scabietic lesions at the classical sites, and absence of a family history of scabies are useful clues to the diagnosis.<sup>20</sup>

## MANAGEMENT

### General Measures

- Treat the patient, household, and close contacts simultaneously regardless of whether they have symptoms of infection or not.<sup>32</sup>
- Before applying the medication a bath or shower is advised. A scrub bath is not indicated, especially prior to application of lindane.
- Drug should be applied to the whole body from neck down. In infants and in patients with CS, the drug should be applied on head and neck also.<sup>33</sup>
- Bedding and clothing should be washed.

## Specific Therapy

Oral and topical antiscabietics are available. The common topical scabicides include precipitated sulfur, tetmosol, crotamiton, benzyl benzoate, lindane, and permethrin. Currently, oral ivermectin has been found to be effective. Precipitated sulfur (as 6% ointment in petrolatum) for three consecutive nights was used in the past. It is very cheap and safe even in infants and pregnant women. It is no longer used because it is messy, stains clothes, and has an unpleasant odor.<sup>33</sup> Tetmosol (tetraethylthiuram monosulfide) as a 25% solution and 5% medicated soap is available but rarely used.

Crotamiton cream or lotion 10% is used, mainly in children. The cure rate is only 60%. It has a good antipruritic action. Single daily application for two consecutive days is recommended. Some suggest that daily application for 5 days may be better than the 2 days currently recommended.<sup>34</sup>

Benzyl benzoate 25% emulsion is widely used in developing countries. It has to be left on the skin for at least 48 hours. It is cheap and effective, but may cause irritation occasionally.<sup>33</sup> Benzyl benzoate may serve a larger role in therapy given the emergence of drug-resistant scabies. It has been found to be effective in permethrin-resistant Norwegian scabies and in combination with ivermectin in patients with relapse after single treatment with ivermectin.<sup>35,36</sup>

### Lindane 1% (Gamma Benzene Hexachloride) Lotion

It is an organochloro compound having miticidal, larvicidal, and ovicidal activity. Lindane is no longer recommended as first-line therapy because of toxicity. It should only be used as an alternative if the patient cannot tolerate other therapies or if other therapies have failed. Lindane resistance has been reported in some areas of the world, including parts of the United States. Lindane should not be used immediately after a bath or shower, and it should not be used by persons who have extensive dermatitis, patients with a history of a seizure disorder, women who are pregnant or lactating, or children aged <2 years of age. Seizures have occurred when lindane was applied after a bath or used by patients who had extensive dermatitis. Aplastic anemia after lindane use also has been reported. If lindane is used, a single overnight application is generally recommended.<sup>33–39</sup>

### Permethrin 5% Cream

Permethrin, a synthetic pyrethroid, is a very effective insecticide used widely in agriculture, livestock, and protection of foods and grains in storage. “Pyrethrum” is the common name for the dried flowers of *Chrysanthemum cinerariaefolium*. “Pyrethrins” are the active insecticidal component of pyrethrum. The identification of the structure of these natural pyrethrins led to the development of synthetic insecticides called pyrethroids.<sup>40</sup>

Although permethrin is highly toxic to arthropods, it is one of the least toxic to mammals. The mean systemic absorption of topical permethrin, over the first 48 hours is approximately 0.5% of the applied dose with a maximum of 2.08% (10% absorption for lindane). As a result, the toxic effects are minimal.<sup>41,42</sup>

Permethrin acts on the parasite’s nerve cell membrane to disrupt the sodium channel current. This causes a delayed repolarization, paralysis, and death.<sup>43,44</sup>

Permethrin is superior to all presently available antiscabietics and is the treatment of the choice in scabies. It has a high cure rate of 91–98%.<sup>42,45</sup> Adverse reactions are few (2%), which include burning sensation, erythema, edema, rash, allergic (to the preservative—formaldehyde) and irritant contact dermatitis.<sup>44</sup> The main advantages are its safety of use even in infants, children, and pregnant women, less expensive than ivermectin, high efficacy and a simple, single, overnight application.

### Ivermectin

Ivermectin is a derivative of a family of macrocyclic lactones, the avermectins, which was found in the fermentation broth of one of the actinomycete cultures (*Streptomyces avermitilis*) received from the Kitasato Institute in Japan. It is named “ivermectin,” because of its action against endoparasites and ectoparasites.<sup>46</sup>

Ivermectin binds selectively and with high affinity to glutamate-gated chloride ion channels, which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions (which is independent of GABA-mediated chloride channels) with hyperpolarization of the nerve or muscle cell resulting in paralysis and death of the parasite. Ivermectin does not readily cross the blood-brain barrier (BBB). This adds to its safety in mammals.<sup>47–49</sup>

The half-life is approximately 12 hours. Ivermectin and its metabolites are excreted mainly in feces (99%). It is active against at least one stage of the life cycle of the parasite. It is effective in nematode infestations, cutaneous larva migrans, onchocerciasis, filariasis, scabies, and head lice infestations.<sup>50,51</sup>

It is available as 3 and 6 mg white scored tablets and also as a liquid preparation for oral and topical use.<sup>52–54</sup> Studies have shown that a dose of 200 µg/kg body weight is effective in scabies, and the cure rates are better, if the dose is repeated after 10–14 days.<sup>55</sup>

No major side effects directly attributable to ivermectin have been observed. The mild and transient side effects include headache, pruritus, rash, arthralgia, and dizziness. Mazzotti reaction, characterized by major features like fever (>40°C), orthostatic hypotension, bronchospasm, neurological deterioration, and minor features like itching, rash, arthralgia, and headache have been observed. This has been linked to a systemic hypersensitivity reaction to dead and dying parasites.<sup>53</sup> One study demonstrated increased mortality among elderly, debilitated persons who received ivermectin, but this observation has not been confirmed in subsequent reports.

It is better avoided in patients with neurological disorders and in those with impaired blood-brain barrier.<sup>56,57</sup> Safety of ivermectin in pregnant women and children below 5 years of age has not been established. However, recent studies report its safe use in children as young as 14 months of age.<sup>58</sup>

The advantages of ivermectin are the simplicity of oral administration, good patient compliance, and safety.<sup>59</sup> Community-



based treatments will be greatly simplified. Crusted scabies associated with HIV infection responds well to ivermectin.<sup>60,61</sup>

### Treatment of Crusted Scabies

Crusted scabies (i.e., Norwegian scabies) is an aggressive infestation that usually occurs in immunodeficient, debilitated, or malnourished persons. Patients who are receiving systemic or potent topical glucocorticoids, organ transplant recipients, mentally retarded or physically incapacitated persons, HIV-infected or human T-lymphotrophic virus-1-infected persons, and persons with various hematologic malignancies are at risk for developing crusted scabies. Crusted scabies is associated with greater transmissibility than scabies. No controlled therapeutic studies for crusted scabies have been conducted, and the appropriate treatment remains unclear. However, observational studies demonstrate the effectiveness of ivermectin for crusted scabies when topical therapies have failed. Substantial treatment failure might occur with a single topical scabicide or with oral ivermectin treatment. Some specialists recommend combined treatment with a topical scabicide and repeated treatment with oral ivermectin 200 µg/kg on days 1, 2, 8, 9, and 15. Additional treatment on days 22 and 29 may be required for severe cases. Ivermectin should be combined with the application of either 5% topical benzyl benzoate or 25% topical permethrin (full body application to be repeated daily for 7 days then 2 × weekly until discharge or cure). Lindane should be avoided because of the risks for neurotoxicity with heavy applications or denuded skin. Patient's fingernails should be closely trimmed to reduce injury from excessive scratching.<sup>39,62</sup> Combination with topical scabicides gives better results along with the standard management of crusted scabies, like nail trimming, applications of keratolytics or antiscabietics in the subungual regions, fomite control, and treatment of all contacts.

### HIV AND SCABIES

Worldwide, there are reports of bizarre forms of scabies occurring in at least 2–4% of patients with HIV infection.<sup>63</sup> The unusual forms of scabies in AIDS can present as crusted scabies or atypical exaggerated scabies. It is common to present initially with ordinary scabies, and as they become progressively immunosuppressed, convert into crusted scabies. In many patients, the pruritus of ordinary scabies lessened or disappeared when the conversion to crusted scabies took place.<sup>64</sup> Crusted or thick whitish-gray plaques, discrete or generalized, in a young patient, should alert the clinician to the possibility of crusted scabies with immunosuppression. Crusted scabies in HIV infection may resemble Darier's disease or psoriasis.<sup>60</sup> The serious problem faced in these patients with crusted scabies is the prominent fissuring leading to bacteremia and death. Wide spectrum of clinical manifestations are seen, with only a few erythematous papules to widespread papules to crusted scabies. The atypical lesions of scabies may resemble pruritus of AIDS, pruritic papular eruption, generalized dermatitis resembling drug

reaction, contact dermatitis or dermatophytosis.<sup>60</sup> Patients with low CD4+ T-cell counts harboring large number of mites present with a diffuse papular eruption referred to as “anergic scabies.” Patients can present with severe pruritus without any clinical signs, but yield numerous mites on scraping. Scabies should be suspected in any atypical itching or asymptomatic rash in patients with HIV/ AIDS. It is very important to prevent the nosocomial spread of scabies from these highly contagious patients. Skin scrapings should be performed and an excellent site for scraping is under the fingernails. HIV-related scabies is more difficult to treat. Ivermectin is the drug of choice in these patients. Concurrent application of a topical scabicide, preferably 5% permethrin cream 2–3 times a week for 6 weeks, gives better results.<sup>60</sup> Concomitant use of keratolytics (3–6% salicylic acid in petrolatum) hastens the removal of crusts.

### Pediculosis Pubis (Phthiriasis)

Pediculosis is an ectoparasitic infestation caused by lice. Human lice belongs to class Insecta, order Phthiraptera and suborder Anoplura. Humans are parasitized by two species, *Pediculus humanus* (head and body louse) and *Phthirus pubis* (pubic louse).

Infestation by pubic louse or crab louse is seen mostly in young adults, transmitted usually by sexual contact. The incidence of the condition increases with increase in the number of sexual partners. It may be acquired by skin-to-skin contact and also from public toilet seats, bathing facility or rarely contaminated bedding or towels. The prevalence seems to be lower in geographic areas where extensive removal of pubic hair, like the “Brazilian wax” is more common. Infection is reported to be more frequent in whites.<sup>65</sup> About 38% of cases with pubic lice have one or more of the other sexually transmitted infections (STIs),<sup>66</sup> which points to its sexual mode of transmission but also indicates a need to screen for other STIs when pubic lice are diagnosed.

### MORPHOLOGY

The pubic or crab louse has a distinct appearance. The adult female louse is dorso-ventrally flattened and has a head with a pair of antennae and mouth parts, a thorax with three pairs of legs each of which ends in a claw, and an abdomen (Fig. 51.8). The pubic louse has a broad, short, grey body, about 1.5–2 mm long. The first pair of legs is more slender than the other pairs. The heavy pincer-like claws help the crab louse to grip adjacent hairs. Eggs are laid in groups of 20–30 and are glued to the hair of the host. Eggs hatch in about 1 week and mature into an adult in 2–3 weeks.

They have a life expectancy of about 1 month.

### CLINICAL FEATURES

Itching in the pubic region is the predominant symptom. Close inspection reveals the presence of lice grasping the pubic hairs close to the skin surface and eggs glued to the hair shafts. The lice are seen mainly in the hair of the pubic region, but in severe



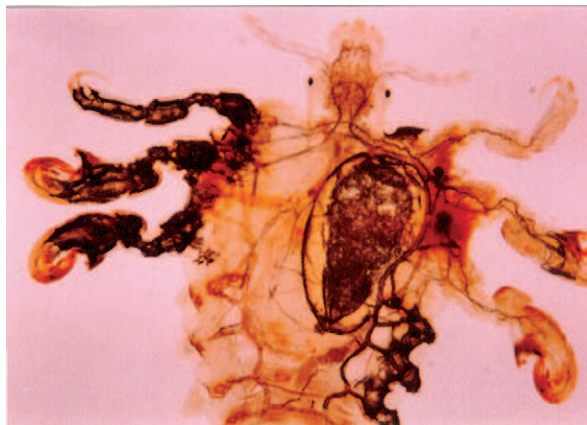


Fig. 51.8: Pubic louse.

cases they may be seen on the hair of moustache, beard, axillae or eyelashes. Scalp hair is usually spared.

Pruritic red papules with central punctum, which becomes excoriated and impetiginized, may also be seen. Bluish and steel grey asymptomatic macules called “maculae cerulae” are useful diagnostic sign. They are more frequently seen on the lower abdomen and thighs.<sup>67</sup> This may be due to an altered blood pigment or a reaction to saliva of the louse. The condition may be asymptomatic in nearly half of the infected cases, as they may not show any reaction to the bite of the louse that may remain attached to the skin, feeding on blood intermittently. It is unable to survive for more than 2–3 days without a blood meal. Severe pruritus and secondary infection may be the only sign of infestation.

The diagnosis is confirmed by demonstrating the louse or nit. The lice are seen as yellowish brown to dark brown specks attached to the base of the hair. The nits are attached to the hair at an acute angle. The presence of pediculosis pubis is an indication to look for other STIs.<sup>68</sup>

## TREATMENT

Gamma benzene hexachloride applied to the entire body below the neck for 12 hours is usually effective. Permethrin 1%, applied for 10 minutes and rinsed off is an effective alternative. There have been some reports of resistance to permethrin and follow-up examinations are indispensable for the clinician to confirm complete removal of crab louse.<sup>69</sup> Benzyl benzoate and crotamiton are other modalities of treatment. Shaving of pubic hair may not be beneficial. Treatment of partner is mandatory as in the case of other STIs. When eyelashes are involved the treatment is rather difficult. Although mechanical removal of lice and eggs with fine forceps or epilation of the lashes with their attached eggs are obvious methods for dealing with eyelash infection, these procedures are uncomfortable and not usually recommended. Several other methods of treating crab lice on the eyelashes have been suggested, including cryotherapy, application of one or two drops of freshly prepared 20% fluorescein eye drops to the lid margin,<sup>70</sup> petrolatum, and physostigmine eye ointment.

Petrolatum can be applied thickly twice daily for a few days. A drawback of physostigmine is that it paralyzes accommodation and causes blurred vision if introduced into the eye. Modern insecticide preparations may be used to treat crab louse on the eyelashes, but alcohol-based preparations are irritant, if inadvertently introduced into the eye, and aqueous preparations such as malathion 0.5% liquid are preferable.

There may be reluctance to accept the use of pesticide creams as treatment for pubic lice. They remain the only effective treatment, other than physical removal of the lice. Health concerns related to the use of topical pesticides and the belief that oral antibiotics are effective therapy are potential barriers clinicians may need to address when treating patients.<sup>71</sup>

## Conclusion

There is an increasing worldwide incidence of scabies and pediculosis. In addition, reports of increasing rate of resistance to commonly used scabicides have become a major issue.<sup>63</sup> Scabies has been classified as a sexually transmissible infection, even though close physical contact without sexual contact is sufficient for transmission. On the other hand, crab louse is usually transmitted by sexual contact. Of the topically applied medications used for scabies, 5% permethrin has been found to be the most effective agent. Lindane is not recommended as first-line therapy because of toxicity. It should only be used as an alternative if the patient cannot tolerate other therapies or if other therapies have failed.

For the treatment of pediculosis, 1% permethrin and pyrethrins with piperonyl butoxide applied to the affected area and washed off after 10 minutes have been found to be most effective. Reported resistance to pediculicides has been increasing and is widespread. Malathion may be used when treatment failure is believed to have occurred because of resistance. All family members and close contacts of patients with scabies or pediculosis should be treated simultaneously. Patients should be informed that post-treatment pruritus can persist for several weeks.

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# section **ix**

## **SEXUALLY TRANSMITTED INFECTION SYNDROMES AND THEIR MANAGEMENT**

— *Antonio Carlos Gerbase*

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# 52

## The Syndromic Approach for the Management of STIs: An Overview

Ahmed S. Latif

### Introduction

Sexually transmitted infections (STIs) are caused by microbial agents that are passed on from person to person at the time of sexual intercourse. STIs are of public health concern not only because of their high prevalence worldwide but also because of their potential to cause serious and permanent complications in persons who are infected and are not treated in a timely and effective way.<sup>1,2</sup> In addition, STIs increase the risk of acquisition and transmission of the human immunodeficiency virus (HIV), the causative agent of AIDS.<sup>3-6</sup>

STIs occur in adults and children. Neonates and infants may become infected as a result of vertical transmission of infection from the mother. Complications of STIs may be serious and include infertility in men and women, an increased risk of ectopic pregnancy in women and blindness and deformities in children. Some complications of STIs in women may be life threatening. Table 52.1 summarizes the complications that may be caused by different STIs. Persons with STIs, both men and women, may remain asymptomatic for varying periods of time and often develop symptoms only when complications occur.

Control of STIs may be achieved through primary or secondary prevention activities. In primary prevention activities, the goal is to prevent the acquisition of STIs through adopting safer sexual behavior and engaging only in safer sex acts. Secondary prevention of the transmission of STIs may be achieved through promoting STI care-seeking behavior, and by rapidly and effectively treating persons with STIs, identifying and treating persons who may have STIs but have only minimal symptoms, and those at greater risk of acquiring STIs.

The objectives of any STI control program are to reduce the incidence and prevalence of STIs, the incidence of STI-related complications, and the sexual transmission of HIV infection.

### Provision of Care for Persons with STIs

High-quality, effective, and acceptable STI care should be available at all health facilities in the private and public sectors and healthcare facilities providing STI care should be accessible

to care seekers. The provision of STI care through categorical STI clinics is at times considered unacceptable as STI care seekers feel stigmatized and fear being identified by the public. This results in the care seeker seeking care elsewhere. Unfortunately, the alternate care providers may not be able to provide the most effective and complete care of the patient. The advantage of having a designated STI clinic is that specially trained personnel and laboratory testing facilities can be made available at the centre and hence all the needs of the care seeker can be met. However, to avoid stigmatization, persons with STIs prefer to attend facilities where they feel that their privacy and confidentiality will be maintained, and they will be treated like any other patient.

STI care is considered acceptable if the care provided is effective in relieving symptoms, preventing complications from occurring, and the care is provided in a non-judgmental and non-moralizing manner without any form of discrimination. It is ideal, therefore, to ensure that all health centers are capable of providing high-quality, acceptable care for persons with STIs. Healthcare providers at the peripheral level, however, often feel that they are unable to provide adequate care as they neither have the expertise or the laboratory facilities to make a correct clinical or

**Table 52.1:** Complications and Causes of STIs

Complications	Causes
Infertility in men and women	Gonococcal and chlamydial infection
Urethral stricture in men	Gonococcal and chlamydial infection
Blindness in infants	Gonococcal infection
Ectopic pregnancy	Gonococcal and chlamydial infection
Pelvic and generalized peritonitis	Gonococcal, chlamydial, anaerobic bacterial infection
Permanent brain and heart disease	Acquired syphilis
Extensive organ and tissue destruction in children	Congenital syphilis
Genital cancer	Human papilloma virus



etiological diagnosis. This is essentially true as making a diagnosis based on finding the etiologic agent causing the infection requires sophisticated laboratory tests and these will not be available at most health centers. Fortunately, however, it is not necessary, in most cases, to make a laboratory-based etiologic diagnosis before providing effective care. In fact, the laboratory tests may even be misleading and may not be able to provide the answers that the healthcare provider is searching for. High-quality, effective STI care may be provided at all health facilities without the need to make a laboratory diagnosis. This may be achieved through the syndromic case management approach.

## Making Diagnosis of STI

The diagnosis of STI may be made in three ways. Firstly, a specific clinical diagnosis may be made after taking a history and examining the patient. From the symptoms and signs, and past clinical experience, a specific diagnosis of the infection is made. Secondly, an etiological diagnosis of STI may be made after positively identifying the causal agent of the symptoms and signs. This requires the taking of specimens from the patient and sending them to a laboratory for appropriate tests. The laboratory will then attempt to identify the pathogen that is causing the symptoms. Thirdly, a syndromic diagnosis of STI may be made after taking a history and examining the patient and identifying the pattern of symptoms and signs that make up a syndrome. This is also a clinical diagnosis.

Each method of making a diagnosis has advantages and disadvantages and these are shown in Table 52.2.

Most commonly throughout the world the diagnostic approaches used include making an etiological diagnosis or making a syndromic diagnosis. The making of a specific diagnosis of an infection through clinical experience is too inaccurate, and hence is not used widely. The diagnostic approaches outlined above are useful if persons present with symptoms and signs related to STIs. However, if a person attends a health facility without any symptoms or signs then the only way to exclude infection is by carrying out laboratory tests.

### MAKING CLINICAL DIAGNOSIS

A clinical diagnosis is made after a history is taken and an examination is carried out. The making of the diagnosis is dependent on the past experience of the clinician. The diagnosis is often inaccurate and different clinical presentations of pathogens may lead to confusion in making a diagnosis. Mixed infections are often missed and a patient may be treated for an infection that he/she does not have. If there is mixed infection the patient may respond partially to treatment and may resume sexual activity with the risk of spreading infection and developing complications.

### MAKING ETIOLOGICAL DIAGNOSIS

In order to make an etiological diagnosis it is necessary to identify the organism that is causing the infection. This requires a laboratory that is capable of carrying out microbiologic and

**Table 52.2:** Advantages and Disadvantages of the Different ways of Making a Diagnosis of STI

Diagnosis	Advantages	Disadvantages
<b>Clinical diagnosis</b>	Patient may be treated for a single infection if the diagnosis is correct	Clinical expertise and experience needed Even with great experience the diagnosis is incorrect in 50% of cases Mixed infections may not be diagnosed Patients may improve transiently and hence could further spread the infection
<b>Etiological diagnosis</b>	Most accurate method of diagnosing a specific infection Treatment may be aimed at a single infection	Need for laboratory capable of identifying and isolating organisms and carrying out blood tests Need for personnel and equipment Need for finances to run the laboratory Expensive Delay in commencing treatment if results of tests are awaited False positive and false negative test results may occur Need for training
<b>Syndromic diagnosis</b>	Allows for diagnosis and treatment at one visit No special tests are necessary to make a diagnosis Diagnosis can be made at all levels of the health infrastructure and a broad range of health workers can use this method Patient can be provided with effective care without delay Simple, inexpensive and reliable Cost effective method of diagnosis	Patient is treated for more than one infection Need for training Possibility of overtreatment as patients will be treated for more than one infection each time

serologic tests on specimens taken from a person who is suspected of having an infection. Table 52.3 shows the tests that need to be carried out in order to establish an etiologic diagnosis and the type of specimen that needs to be submitted to the laboratory. Provided that the clinic has some laboratory equipment and personnel trained and experienced in performing tests, it may be possible to carry out some of the tests while the patient waits at the clinic. The tests that may be performed quickly and reliably at the clinic include:

- Gram-staining and microscopy
- Microscopic examination of fresh wet mounts of secretions

**Table 52.3:** Laboratory Tests Needed to be Performed in Order to Establish an Etiologic Diagnosis of STI

Diagnosis	Specimens needed	Tests to be carried out
<b>Early syphilis</b>	Fresh exudates from moist lesions or lymph node aspirates Venous blood	Dark field microscopy to identify <i>T. pallidum</i> Serological tests for syphilis
<b>Latent syphilis</b>	Venous blood	Serological tests for syphilis
<b>Chancroid</b>	Fresh ulcer exudates or bubo aspirates	<i>H. ducreyi</i> culture and identification Nucleic acid amplification tests for detecting <i>H. ducreyi</i> nucleic acid
<b>Gonorrhea</b>	Smears and swabs of urethral discharge and cervical discharge	Microscopy of gram stained smears of discharge <i>N. gonorrhoeae</i> culture and identification Nucleic acid amplification tests for detecting <i>N. gonorrhoeae</i> nucleic acid
<b>Chlamydial infection</b>	Smears and swabs of urethral discharge and cervical discharge	Antigen detection by fluorescent microscopy <i>C. trachomatis</i> culture and identification Nucleic acid amplification tests for detecting <i>C. trachomatis</i> nucleic acid
<b>Granuloma inguinale</b>	Deep smears of ulcer exudates or biopsy of ulcers	Microscopy of Giemsa stained smears Nucleic acid amplification tests for detecting <i>K. granulomatis</i> nucleic acid Histology of tissue biopsies
<b>Genital herpes</b>	Smears and swabs of ulcer exudates	Antigen detection by fluorescent microscopy Antigen detection by ELISA tests Herpes simplex culture Nucleic acid amplification tests for detecting herpes simplex virus nucleic acid
<b>Trichomoniasis</b>	Fresh swabs of genital discharge	Microscopy of wet preparations <i>T. vaginalis</i> culture and identification
<b>Candidiasis</b>	Smears and swabs of genital discharge	Microscopy of gram-stained smears of discharge <i>C. albicans</i> culture and identification
<b>Bacterial vaginosis</b>	Fresh swabs of genital discharge	KOH test Microscopy of gram-stained smears Anaerobic culture of material (Note: Clinical criteria are necessary)

- Rapid plasma regain (RPR) test—a non-specific test for syphilis performed on patients' serum
- Rapid specific test for syphilis—a number of rapid tests for syphilis are now available commercially

- A urine examination for polymorphonuclear leukocytes by using the leukocyte esterase (LE) dip stick method. This test provides indirect evidence for gonococcal and/or chlamydial urethritis in men; the test however is neither sensitive nor specific for these infections.

The laboratory technologist at the clinic can also ensure that the specimens that are to be sent away for tests at another laboratory are properly catalogued, labeled, and packaged for transport.

Making an etiologic diagnosis of STI is associated with a number of problems. It requires a well-equipped laboratory and trained personnel. Laboratory testing costs money and tests take time to be carried out and therefore there are delays in commencing treatment. Tests available are not foolproof and the sensitivity and specificity of commercially available tests varies significantly. This affects the reliability of tests in making an accurate diagnosis. In addition, there is a need to establish strict external quality control measures. Currently only gram-stain and microscopy, urine microscopic examination, and non-specific syphilis serology can be performed at primary care clinics in most developing countries. The availability of rapid specific tests for syphilis is improving in many countries and this will improve testing for syphilis at the first point of care.

### MAKING SYNDROMIC DIAGNOSIS

The syndromic approach to the diagnosis of STIs is based on the fact that a number of sexually transmissible pathogens produce a common pattern of easily recognizable symptoms and signs. This approach in making a diagnosis of STI is only applicable to those persons with STI who present with symptoms and signs. Since making a syndromic diagnosis is based on the presence of symptoms and/or signs this approach is not applicable in persons with infection who are asymptomatic.

In persons with symptoms and signs this approach is most useful in terms of practicability and in terms of cost effectiveness. Sexually transmissible pathogens produce a small number of syndromes. The syndromic management of STI is based on the identification of the STI-related syndrome, and the provision of treatment that will deal with the majority or most serious organisms responsible for producing a syndrome. The syndromes and their causes are shown in Table 52.4.

Infection with most of the sexually transmissible pathogens results in the development of a pattern of symptoms and signs. A collection of symptoms and signs, resulting in a clinical pattern, is known as a syndrome. It is not difficult clinically, therefore, to recognize an STI by the clinical syndrome it produces. Though STIs are caused by a large number of different pathogens, a number of these different pathogens produce a common set of symptoms and signs.

As an example, it is known that a common cause of urethral discharge in men is *Neisseria gonorrhoeae*, the causal agent of gonorrhea. However, it cannot be stated that if a man has a urethral discharge then he always has gonorrhea. We know that urethral discharge may be caused by pathogens other than those that cause

**Table 52.4:** STI-Related Syndromes and Their Causes

STI syndrome	Causes of the syndrome
Urethral discharge	<i>N. gonorrhoeae</i> , <i>C. trachomatis</i>
Genital ulcers	<i>T. pallidum</i> , <i>H. ducreyi</i> , Herpes simplex virus, <i>K. granulomatis</i> , <i>C. trachomatis</i>
Vaginal discharge syndrome	<i>N. gonorrhoeae</i> , <i>C. trachomatis</i> , <i>T. vaginalis</i> , <i>C. albicans</i> , and anaerobic bacteria
Suppurative inguinal lymphadenitis (Bubo)	<i>H. ducreyi</i> , <i>C. trachomatis</i>
Lower abdominal pain (women)	Pelvic inflammatory disease – caused by <i>N. gonorrhoeae</i> , <i>C. trachomatis</i> and other bacteria
Acute scrotal swelling	<i>N. gonorrhoeae</i> , <i>C. trachomatis</i> and other bacteria and viruses
Neonatal purulent conjunctivitis (ophthalmia neonatorum)	<i>N. gonorrhoeae</i> , <i>C. trachomatis</i> and other bacteria

gonorrhea. These include *Chlamydia trachomatis*, *Trichomonas vaginalis*, and *Mycoplasma genitalium*. All these are organisms that can cause urethral discharge in men. It can therefore be stated that the syndrome of urethral discharge may be caused by any of these pathogens. In order to determine the exact cause of the discharge, laboratory tests need to be carried out. The tests that are needed are complicated to perform, expensive, and it may take some days for the results to become available. The patient can neither wait for the results before he is treated, nor should he wait. As we know that a number of different organisms can cause the symptoms and signs the best thing to do is to treat the patient for all the organisms that are known to cause the syndrome. But this would be unacceptable overtreatment. In practice what we do, however, is give the patient treatment for the common causes of urethral discharge in the country or region. We know from studies carried out that the common causes of urethral discharge are *N. gonorrhoeae* and *C. trachomatis*. Therefore, all men who come to us with urethral discharge syndrome we will treat for gonococcal and chlamydial infection in the first instance. In this way the patient is not only relieved of his symptoms, but he is also rendered non-infectious as quickly as possible, and the risk of him developing complications and further transmission is reduced.

Similarly for persons presenting with genital ulcers a diagnosis of genital ulcer syndrome is made; the common causes of genital ulcer syndrome are genital herpes, syphilis and chancroid, though in some parts of the world other causes of genital ulcers such as granuloma inguinale (Donovanosis) and lymphogranuloma venereum are also commonly found. It is important therefore that epidemiologic studies are carried out periodically.

### RISK ASSESSMENT IN MAKING DIAGNOSIS OF STI

In order to assist in making a diagnosis of STI, it may be possible to carry out a risk assessment for STIs. In general it may be assumed that persons with STI have engaged in risky sexual behavior and risky sexual activity. Any person who has

unprotected sexual intercourse with a non-regular partner has placed himself/herself at risk for STI. Similarly, any person who has multiple sexual partners, engages in frequent partner change, engages in commercial sexual activity or has sex with a partner who has an STI, is at risk for acquiring STIs.

By carrying out a risk assessment it may be possible to make a diagnosis of STI with greater certainty and provide appropriate care to patients. Risk assessment is particularly useful when managing women with vaginal discharge: women with vaginal discharge may have vaginitis, which is caused by trichomoniasis, candidiasis or bacterial vaginosis, or, they may have cervicitis, which is caused by gonococcal or chlamydial infection. Commonly, women with vaginal discharge have both vaginitis and cervicitis. Clinically it is extremely difficult to distinguish between the two main causes of vaginal discharge especially since both causes may be present. Vaginitis is the usual and more frequent cause; however, cervicitis is the more serious cause as the pathogens that cause cervicitis can lead to serious complications. A thorough clinical examination will also not help in excluding vaginitis from cervicitis. Apart from carrying out complex laboratory tests, there is no easy method of distinguishing between vaginitis and cervicitis.

Studies have shown that in women with vaginal discharge the following risk factors are indicative of the presence of cervicitis:

- The partner has an STI
- The patient is aged less than 21 years
- The patient is not married
- The patient has had sexual contact with a new partner in the last 3 months
- The patient has had sexual contact with more than one partner in the last 3 months

These risk factors are not universally applicable and vary from place to place. There is a need to determine locally the risk factors associated with cervicitis in women with vaginal discharge. However, until such time that local risk factors have been identified it is advisable to use the risk factors listed above. It is recommended that a woman with vaginal discharge be considered to have a positive risk assessment for cervicitis if she admits that her partner has an STI or if she has any other two of the risk factors listed above. Hence, all female sex workers with vaginal discharge are risk-assessment positive for cervicitis and should be treated. The use of risk factors in asymptomatic subjects has not been evaluated extensively. There is a need for more studies to be carried out in order to address this problem.

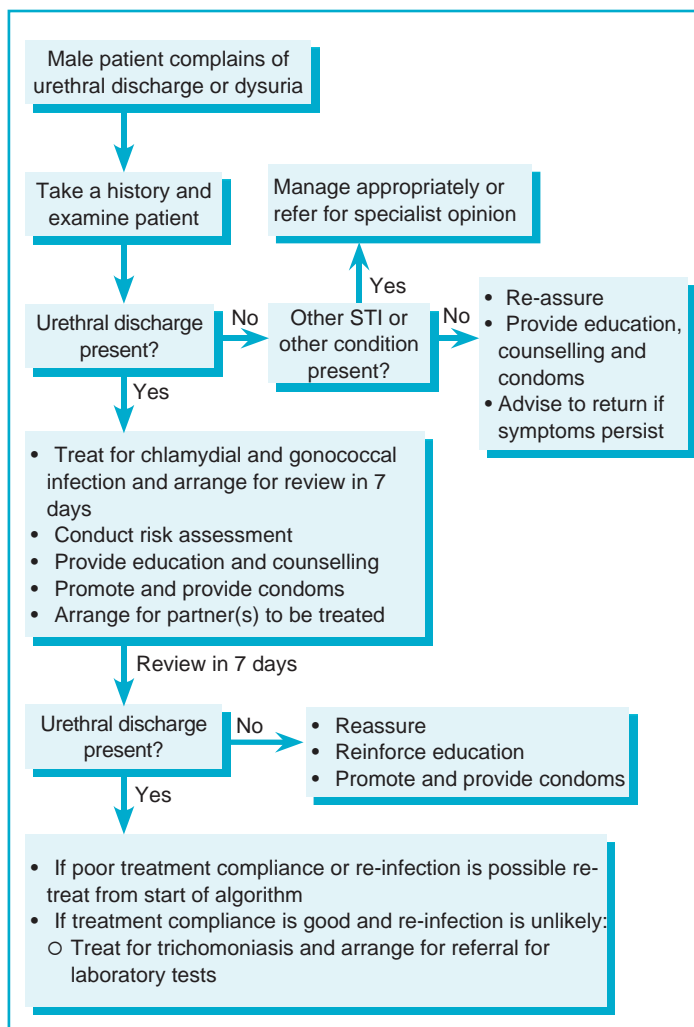
### Syndromic Case Management of STIs

Once a syndromic diagnosis of the STI is made, the patient may be offered treatment. However, the simple provision of antibiotics is not enough. All patients with STIs should be given the complete care “package”. Patients with STIs have become infected through their own or their partner’s risky sexual behavior and have placed themselves at risk of becoming infected with HIV as well. All healthcare providers should take advantage of the STI consultation to provide the patient



with the means of avoiding becoming infected in the future. Regardless of the manner in which the diagnosis of STI has been made (i.e., syndromic or etiologic) all patients with STIs should be offered as a minimum:

- Appropriate antibiotic treatment for the infection diagnosed or for the STI syndrome diagnosed
- Health education on the nature of the infection
- Health education on ways to avoid becoming infected in the future through safer sexual behavior and safer sex activity
- Counseling after an assessment of the patient's own perception of risk for STI and reasons for risk-taking
- Health education on the importance of treatment compliance
- Education on the correct use of condoms
- A supply of condoms
- Information on how the patient's partner(s) can also be treated
- Testing for HIV after pre-test information has been given
- A date for a follow-up examination when the patient is examined, results of tests, if performed, are discussed, and education is reinforced

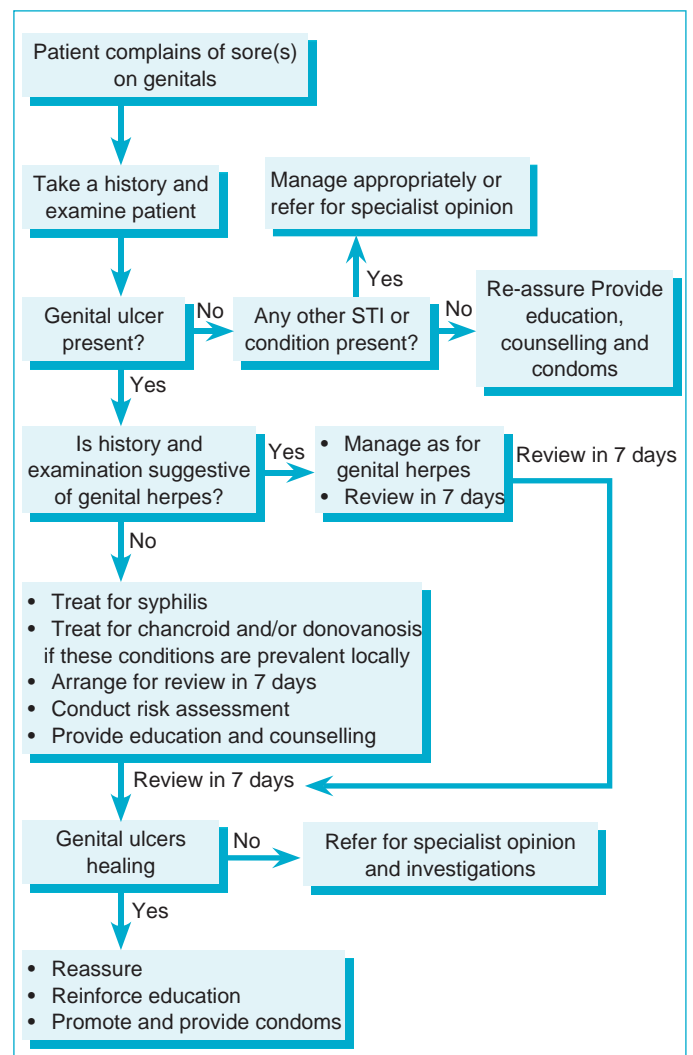


**Fig. 52.1:** Algorithm for the diagnosis and management of urethral discharge in men.

## MANAGING STI SYNDROMES

Simple clinical management flowcharts may be used to guide healthcare providers in managing patients with STI syndromes. Figures 52.1 and 52.2 are examples of clinical management algorithms for two common STI-related syndromes, urethral discharge in men, and genital ulcers in men and women.

Similar clinical management algorithms have been developed for most STI-related syndromes; however, one common syndrome, vaginal discharge in women, is quite complex and needs to be adapted locally in response to local prevalence of infections that cause vaginal discharge. Vaginal discharge may be physiologic or pathologic. Physiologic vaginal discharge is a normal state and does not require treatment. It appears at various times during the menstrual cycle, before, during, and after sexual intercourse, and during pregnancy and lactation. Therefore all women should be carefully evaluated if they present with a vaginal discharge. An abnormal or pathologic vaginal discharge may be caused by vaginitis, cervicitis and infection of the genital tract above the



**Fig. 52.2:** Algorithm for the diagnosis and management of genital ulcer syndrome in men and women.

cervix, that is, pelvic inflammatory disease (PID). In women with symptomatic vaginal discharge it is important to attempt to distinguish whether the patient has vaginitis or cervicitis. From the clinical examination alone it may not be possible to differentiate between these. Vaginitis is generally caused by trichomoniasis, candidiasis and bacterial vaginosis; though other, less common, causes of vaginitis should be kept in mind. Cervicitis is caused by gonococcal or chlamydial infection and other STIs such as genital herpes, genital warts and other cervical lesions. Developing syndromic protocols for management of vaginal discharge that are sensitive and specific for STIs in a range of settings has proven more difficult.

The World Health Organization (WHO) advises that in women with vaginal discharge a rapid behavioral and demographic screen should be carried out and has identified certain factors that are predictive for cervicitis.<sup>7</sup> These risk factors are:

- The partner has an STI
- The patient is aged less than 21 years
- The patient is not married
- The patient has had sexual contact with a new partner in the last 3 months
- The patient has had sexual contact with more than one partner in the last 3 months

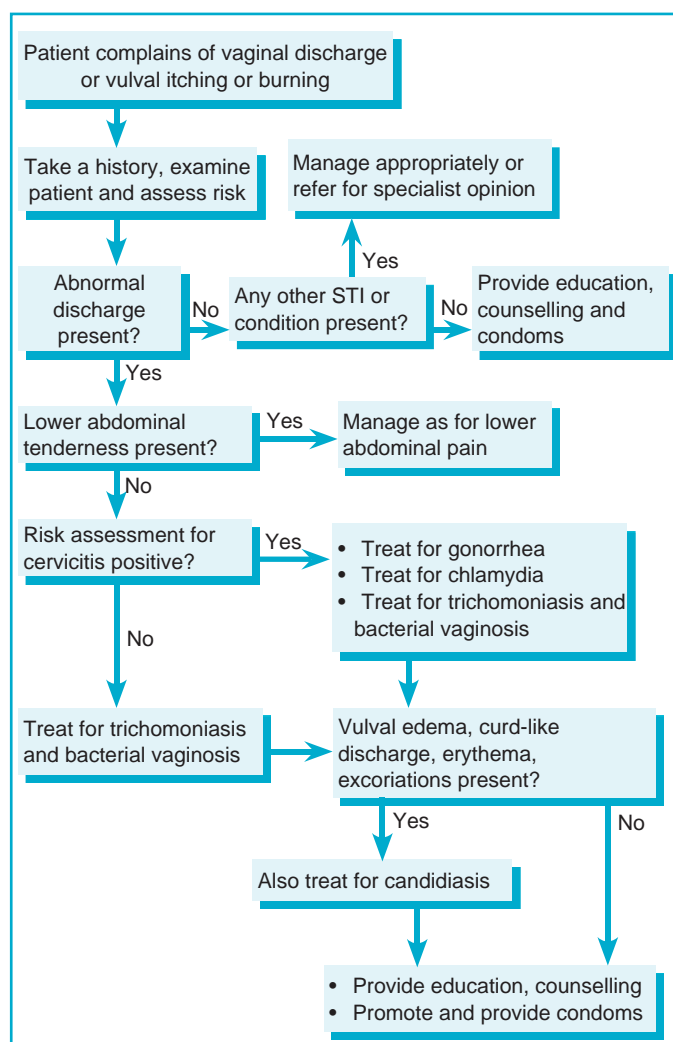
WHO advises that a woman with vaginal discharge has a positive risk assessment for cervicitis if she states that her partner is symptomatic or if she has any two of the other risks listed. An algorithm for the diagnosis and management of vaginal discharge based on risk assessment is shown in Figure 52.3.

Syndromic management algorithms for managing vaginal discharge when it is possible to carry out simple laboratory tests have also been developed<sup>3</sup> and WHO has also developed algorithms for use when a speculum examination is possible. A clinical management algorithm for the management of lower abdominal pain and tenderness is shown in Figure 52.4. It should be noted that lower abdominal pain in women may indicate a serious, life-threatening illness and in making recommendations for the management of women with such symptoms and signs causes such as acute appendicitis, ectopic pregnancy and complications of pregnancy should be addressed.

In men and women presenting with discharge dual treatment for gonorrhea and chlamydia is now widely recommended since affordable single-dose therapy with minimal side effects is available to treat both infections adequately and also because the two infections often co-exist. Syndromic management protocols will vary according to local patterns of infection and antibiotic susceptibility of microorganisms responsible for the symptoms and signs.

### Management of Urethral Discharge in Men

Common causes of urethral discharge in men include *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. In the syndromic



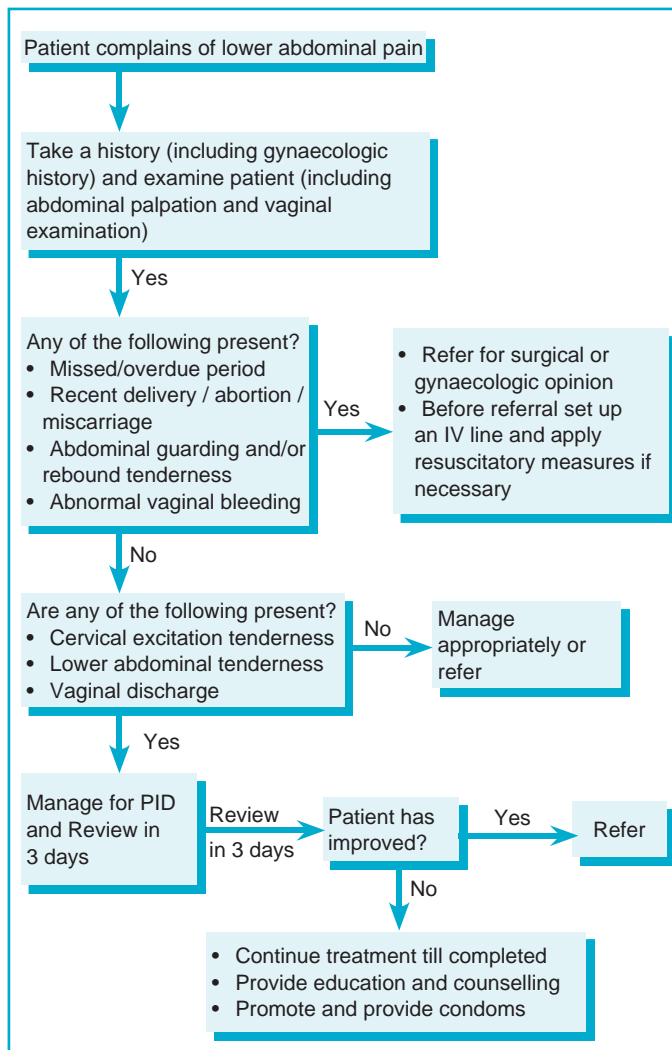
**Fig. 52.3:** Algorithm for the diagnosis and management of vaginal discharge in women.

management of men with urethral discharge, treatment should adequately cover these two organisms. A history should be taken, and the patient should be examined to determine whether urethral discharge is present or whether there is any other STI. If urethral discharge is found then the patient should be treated for gonorrhea and chlamydia. If any other STI is found the patient should be treated appropriately.

For treatment of individual infections please refer to Chapter 54.

### Management of Persistent or Recurrent Urethral Discharge in Men

Urethral discharge in men may persist or recur. If a person has been treated adequately for urethral discharge and presents with a recurrence or persistent discharge the reasons may be that he has become re-infected, he has not taken his treatment as prescribed, he has a resistant infection, or that the cause



**Fig. 52.4:** Algorithm for the diagnosis and management of lower abdominal pain and tenderness in women.

of the infection may not have been gonococcal or chlamydial infection. Men with recurrent or persistent symptoms should be examined to confirm that they do have a discharge. If a urethral discharge is present the patient should be re-treated if it is likely that re-infection or poor treatment compliance has occurred or given treatment for trichomoniasis if re-infection is unlikely and treatment compliance has been adequate. At this point it is worthwhile to take urethral specimens for laboratory examination.

### Management of Vaginal Discharge in Women

Women presenting with a history of vaginal discharge should have a history taken, a risk assessment for cervicitis carried out, and should also be examined. If it is possible a speculum examination should be performed. A spontaneous complaint of abnormal vaginal discharge, that is, abnormal in terms of quantity, color or odor, is most commonly due to a vaginal infection. Rarely, it may be the result of mucopurulent STI-

related cervicitis. *Trichomonas vaginalis*, *Candida albicans* and bacterial vaginosis are the commonest causes of vaginal infection while *N. gonorrhoeae* and *C. trachomatis* cause cervical infection. The clinical detection of cervical infection is difficult because of the asymptomatic nature of gonococcal or chlamydial cervical infection. The symptom of abnormal vaginal discharge is highly indicative of vaginal infection, but poorly predictive for cervical infection.<sup>3</sup> The WHO recommends that all women presenting with vaginal discharge should receive treatment for trichomoniasis and bacterial vaginosis, in addition those women who have a positive risk assessment for cervicitis should be treated for gonococcal and chlamydial infection as well. In women with vaginal discharge, if there is vulval edema, a curd-like discharge, vulval excoriations or erythema, treatment for candidiasis should also be given.

### Management of Genital Ulcers in Men and Women

The prevalence of pathogens responsible for genital ulcer disease varies considerably according to the geographic region. The clinical differentiation of cause of genital ulcers is inaccurate, hence management of genital ulcers is based on an understanding of the epidemiology and etiology of genital ulcers locally and recommendations should be based on local patterns of disease prevalence. In areas where both syphilis and chancroid are prevalent, it is advisable to treat all patients with genital ulcers for both conditions initially. In areas where granuloma inguinale is also prevalent, treatment for this condition should be included. In many parts of the world, genital herpes simplex virus infection has become the commonest cause of genital ulcers especially in areas where HIV prevalence is high. A number of studies have shown the benefits of adding herpes virus treatment when treating patients for genital ulcer disease. This form of episodic treatment of herpes simplex virus infection relieves the symptoms and promotes healing of lesions, thereby shortening the duration of the episode.

### Management of PID

PID is caused by infection ascending from the lower genital tract and organisms responsible include *N. gonorrhoeae*, *C. trachomatis*, and anaerobic bacteria. PID implies endometritis, salpingitis, oophoritis, and pelvic peritonitis. Women with PID have lower abdominal pain, vaginal discharge, irregular menstruation, dyspareunia, and may have fever and diarrhea. On examination there is tenderness on palpation of the lower abdomen and pelvis and digital vaginal examination will reveal cervical excitation tenderness and vaginal discharge.

Women with lower abdominal pain and/or tenderness should be examined carefully to exclude surgical or gynecologic conditions requiring immediate referral for specialist care. If the patient needs to be resuscitated then resuscitator measures should be applied before transfer and an intravenous line should be set



up. The following women with lower abdominal pain and/or tenderness should be referred for specialist opinion:

- the diagnosis is uncertain;
- surgical emergencies such as appendicitis and ectopic pregnancy cannot be excluded;
- there is a history of recent abortion, miscarriage or delivery;
- there is abdominal guarding and rebound tenderness or a mass in the pelvis suggesting pelvic peritonitis or a pelvic abscess;
- severe illness precludes management on an outpatient basis;
- the patient is pregnant;
- the patient is unable to follow or tolerate an outpatient regimen; or
- the patient has failed to respond to outpatient therapy.

Women who have acute PID and are not in any of the above categories should receive treatment for gonococcal, chlamydial, and anaerobic bacterial infection.

### Management of Acute Scrotal Swelling

Acute epididymo-orchitis should be suspected in all men presenting with acute scrotal swelling and pain. However other causes, including surgical emergencies such as testicular torsion, traumatic hematocele, and irreducible or strangulated inguinal herniae, should be excluded through careful history taking and examination. In men with acute epididymo-orchitis treatment for gonorrhea and chlamydial infection should be given. As acute epididymo-orchitis may occur as a result of bacterial infection of the urinary tract some experts believe that persons over the age of 49 years should first receive treatment for urinary tract infection as well.

### Management of Suppurative Inguinal Lymphadenitis (Bubo)

Inguinal and femoral buboes are enlargements of the lymph nodes in the inguinal regions and the femoral triangles of the body. They are caused by inflammation of lymph nodes and may lead to the formation of unilocular or multilocular abscesses. Buboes are frequently associated with lymphogranuloma venereum and chancroid. However buboes may occur in non-STIs as well, including infected lesions on the lower extremities and in some systemic infections as well. Patients with buboes should be treated for chancroid and lymphogranuloma venereum and if genital ulcers are present for syphilis as well.

### Management of Sexually Transmitted Anorectal Infections

Anorectal symptoms including anal discharge and pain are frequently encountered in men who have sex with men and in female sex workers. Gonorrhea, chlamydia, herpes simplex virus infection, and syphilis are the common causes of anorectal STIs. Symptoms associated with anorectal STIs include rectal and anal

pain, pruritus, anal discharge, anal bleeding, sensation of rectal fullness, and tenesmus, constipation, and mucous streaking of the stools. Patients with such symptoms should be carefully examined and should have anoscopy or proctoscopy performed. A high index of suspicion is needed when managing patients who have had receptive anal sex.

Patients with such symptoms should be treated for gonorrhea and chlamydial infection and if they have a genital ulcer or anal pain they should receive in addition treatment for syphilis and herpes simplex virus infection.<sup>8–10</sup>

### PROVISION OF COMPREHENSIVE STI CARE

The simple provision of antibiotics for an STI is not sufficient. The STI consultation provides an ideal opportunity to institute interventions to prevent the future acquisition of infection and to prevent further transmission. The patient-clinician encounter should be used as an opportunity to provide education on the nature of infection, and its mode of transmission and possible complications. In addition, during the encounter the patient's perception of risk and reasons for engaging in unsafe activity should be assessed and then the patient should be counseled on risk reduction. The patient should also be educated on the correct use of condoms, and the association between STIs and HIV infection. Finally, the patient should be educated on how to prevent becoming infected in future through modifying sexual behavior, that is, sexual abstinence, having sex only with a mutually faithful lifelong partner, or using condoms. It is important to bear in mind that patients with STI have put themselves at risk of becoming infected with HIV as well. The time of the consultation is an opportune moment to offer health education.

The components of comprehensive STI care are as summarized below:

- Making a diagnosis of STI after taking a history and carrying out a physical examination
- Providing antibiotics for the STI syndrome and educating the patient on the importance of treatment compliance
- Providing education on the nature of infection, possible complications, modes of transmission and prevention, and association between STIs and HIV infection
- Education on the correct use of condoms and providing the patient with condoms
- Assessing the reasons for risk taking behavior and providing counselling on risk reduction
- Education on the importance of abstaining from sexual activity until cured
- Education on the importance of attending for a follow-up examination and providing the patient with a date for follow-up attendance
- Educating on the importance of having all contacts examined and treated and initiating partner notification and contact tracing activities

## PROVISION OF EDUCATION

As part of syndromic case management all patients with STIs and those in whom the diagnosis of STI is considered should receive education on the prevention of STIs. The following education messages should be delivered during the consultation:

### Modes of Transmission of STIs and the Nature of Infection

Patients with STI should understand that infection is acquired through unprotected sexual intercourse and that there are ways to prevent becoming infected in future. These include abstaining from sex, engaging in sex with a faithful partner or using condoms when having sex.

The nature of the infection and the possible complications should also be explained. Patients should understand the seriousness of STIs. It has been established that HIV infection, the causal agent of AIDS, is an STI and is acquired in the same way as other STIs. Hence persons who engage in unprotected sex can easily become infected with HIV. Patients should also be informed that all STIs facilitate the transmission of HIV. Patients should be made aware of the fact that some STIs can cause permanent and irreversible complications such as infertility in men and women, ectopic pregnancy and serious intra-abdominal infection in women, fetal infections and blindness in neonates.

### Adherence to Treatment and Follow-up Examination

The importance of adhering to treatment and completing the full course of treatment should be emphasized. Patients should be made to understand that failure to comply with treatment may lead to complications and a reduced response to re-treatment as drug resistance may develop. Patients should refrain from sexual activity altogether while taking treatment and until they are cured. All patients should be encouraged to attend for a follow-up examination when results of tests are discussed and education is reinforced.

### Condom Promotion and Provision

Patients, males and females, should be educated on the correct use of condoms. A demonstration of the correct use of a condom should be carried out using a penis model. Patients should also be told of how to hygienically dispose of used condoms. Female condoms are now available for women to use and these allow the woman to protect herself especially when her male partner is reluctant to use a male condom. Patients should be provided with a supply of condoms at the time of the consultation and should be advised where condoms can be obtained in future.

## Partner Notification and Treatment

Provide education on the importance of partner notification and treatment. The patient should understand that in order to break the cycle of STI transmission and preventing re-infection it is important to treat not only the index presenting with infection but also the source contact and any secondary contacts that the patient may have infected after acquiring the infection. Patients should understand that many STIs remain in the body without producing any symptoms and that infected persons often do not know that they have an infection until a contact informs them. In order to reach contacts the full cooperation of the index patient is necessary. Different methods of partner treatment have been developed. Partner notification may be index patient facilitated or provider facilitated. Patient facilitated partner notification is an exercise in which the patient informs his/her partner(s) to seek care. In this method the index is provided with contact tracing cards which he/she passes on to the partners. In the provider facilitated method details of contacts are obtained from the index and then the health services seeks out the contacts. This latter method is resource intensive and is often used for a limited number of the more serious infections. Currently patient delivered partner treatment is being evaluated. In this method the index is provided with treatment for the partner and is left to his/her own resources to give the partner the treatment.

The success of partner notification and treatment programs depends on the trust and confidence that the patient has in the health service. It cannot be over-emphasized that persons with STIs are treated with respect and that healthcare provider attitudes are non-moralizing and non-judgmental and that confidentiality and privacy are assured at all times. The system of partner referral and treatment that is used depends on the setting, the resources available, and the level of prevalence of infection in a specific community.

### ASSESSING THE PATIENT'S PERCEPTION OF RISK

In order to modify sexual behavior it is necessary to assess the factors that led the patient to engage in risk-taking activity. Factors commonly associated with risky sexual behavior include, separation from the marital partner, travel away from home, economic needs, alcohol and drug use, and peer pressure. Once the possible reasons for unsafe behavior have been determined then the patient may be counseled on ways of coping with such situations. In order to modify sexual behavior it is important to find out whether the patient perceives himself/herself to be at risk of infection. Patients who engage in casual unprotected sex should be encouraged to attend for care if any of the factors listed above apply to them. The asymptomatic nature of STIs should also be explained to patients.

## PROVISION OF ACCESSIBLE AND ACCEPTABLE CARE

High-quality, effective, and acceptable STI care should be available at all health facilities in the private and public sectors and healthcare facilities providing STI care should be accessible to care seekers. The provision of STI care through categoric STI clinics is at times considered unacceptable as STI care seekers feel stigmatized and fear being identified by the public. This results in the patient seeking care elsewhere. An advantage of having categoric STI clinics is that specially trained personnel and laboratory testing facilities can be made available at the centre and hence all the needs of the care seeker can be met. In order to avoid stigmatization, persons with STIs prefer to attend facilities where they feel that privacy and confidentiality will be maintained and where they will be treated like any other healthcare seeker.

STI care is considered acceptable if the care provided is effective in relieving symptoms, preventing complications from occurring, and the care is provided in a non-judgmental and non-moralizing manner without any form of discrimination. It is ideal, therefore, to ensure that all health centers are capable of providing high quality, acceptable care for persons with STIs. Healthcare providers often feel that they are unable to provide adequate care for persons with STIs as they do not have the expertise or the laboratory facilities to make a diagnosis of STI. This is essentially true as making a diagnosis based on finding the etiologic agent causing the infection requires sophisticated laboratory tests and these will not be available at most health centers. Fortunately, however, it is not necessary, in most cases, to make a laboratory-based etiologic diagnosis before providing effective care. High-quality, effective STI care may be provided at all health facilities without the need to make a laboratory diagnosis. This may be achieved through the syndromic case management approach.

Persons with STIs often do not seek care as they feel that they may be stigmatized and discriminated against at health facilities. All health facilities should provide care for persons with STIs that is both accessible (i.e., affordable, within easy reach from home or workplace, and available at times convenient for the patient), and, acceptable (i.e., effective, non-stigmatizing, and non-discriminating).

## Summary

The syndromic case management of persons with STIs is a useful and practical way to provide high quality, effective and acceptable care for persons with STIs. Such care should be available at all health facilities. The provision of STI care should be integrated within primary healthcare facilities, maternal and child health facilities and family planning clinics. There is a need to train all healthcare providers in the syndromic case management approach. The training should be incorporated in the training curricula of medical students and basic and post basic nurses. Studies need to be carried out on a regular basis in order to monitor the antimicrobial susceptibility of etiologic agents and the change in the pattern of prevalence of STIs. Studies also need to be carried out to determine the demographic and behavioral risk factors associated with STIs.

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# 53

## Genital Ulcer-Adenopathy Syndrome

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### Introduction

Genital ulcer-adenopathy syndrome is generally a presentation of some sexually transmitted infections and rarely few other dermatological/systemic conditions. Five important sexually transmitted pathogens cause the syndrome of genital ulcer disease (GUD), namely, *Treponema pallidum* (causing syphilis), *Haemophilus ducreyi* (causing chancroid), *Chlamydia trachomatis* strains L1-L3 (causing lymphogranuloma venereum), *Klebsiella granulomatis* (causing donovanosis), and herpes simplex virus type 2 (causing genital herpes). Since the prevalence of these pathogens varies by geographical settings and their epidemiology changes over time, it cannot be emphasized enough that any treatment protocol needs to respond to the locally prevailing epidemiology and the antimicrobial susceptibility patterns of the organisms. Definitive laboratory-based etiological diagnosis will require substantial financial and human resources which are not available in many situations. Additionally, even with syphilis, for which a laboratory test is the cheapest and simplest to perform, about 30% of patients will have a non-reactive non-treponemal test in early primary syphilis, i.e., the stage of the ulcer.<sup>1</sup> Furthermore, a reactive syphilis serology test does not necessarily mean that the etiology of the current ulcer is *T. pallidum*, especially in settings where there is a high prevalence of false-positive syphilis serology in the general population due to other diseases caused by spirochaetes, viz. yaws and pinta.

The common practice of a physician's clinical diagnosis of GUD has been shown to be inaccurate in a number of studies. The inaccuracy is due to a number of factors, including mixed infections, atypical appearance or simply similarities in appearance between ulcers caused by one or the other pathogen. Studies undertaken in Johannesburg, South Africa, demonstrated an accuracy of 55% for syphilis and 22% for genital herpes based on a clinical diagnosis. In another study using PCR techniques, syphilis and genital herpes were both under-diagnosed giving a clinical diagnosis sensitivity of 31% and 47%, respectively, whereas syndromic management protocols provided adequate treatment for 90% of patients with GUD in that setting.<sup>2-4</sup> Therefore, in the

absence of a cheap, reliable multiplex test for GUD, syndromic management seems to offer the next best option. This approach works equally well for men and women with ulcerative disease. In much the same manner as for urethritis in men, WHO has recommended the syndromic management protocols for GUD in both men and women.

### Epidemiology of Genital Ulcers

The relative prevalence of sexually transmitted pathogens that cause genital ulcers varies widely from country to country and within countries. Thus, it is important to conduct etiological studies to determine what the prevailing pathogens in a particular country of setting are. Table 53.1 shows some data collected from different geographic regions between 1998 and 2010 using molecular diagnostic tests, which are more sensitive and, in many cases, more specific than conventional laboratory methods for the detection of sexually transmitted infections.<sup>5,6</sup> The diagnosis of donovanosis and LGV, however, is usually made from clinical appearance, and there may be considerable under-reporting of these infections.

### Genital Herpes

Genital herpes caused by herpes simplex virus (HSV) type 1 or 2 is the most common cause of GUD globally and is a cofactor in HIV acquisition and transmission. The incidence of genital herpes is on the rise in most countries, and in many countries it has become the most common cause of genital ulceration. The majority of patients infected with HSV type 1 or 2, may not be aware of their infection because the infection is either asymptomatic or sub-clinical or unrecognized. Since asymptomatic or sub-clinical genital viral shedding can occur, HSV infection may be transmitted unknowingly to sexual partners.

### PATHOGENESIS

HSV infection occurs when viral particles enter the skin or mucous membranes through microscopic abrasions. Entry of

**Table 53.1:** Etiology of Genital Ulcers in Various Countries<sup>7–18</sup>

Countries (Year)	Diagnostic tests	Genital Herpes (%)	Syphilis (%)	Chancroid (%)	Donovanosis (%)	LGV (%)	HIV seroprevalence in all patients with genital ulcers (%)
France (2010) <sup>7</sup>	PCR, culture, serology	27	35	3			27
Tanzania (2003) <sup>7</sup>	PCR	49	1	12	—*	—*	50
Dominican Republic (2002) <sup>8</sup>	PCR	43	5	26	—*	—*	—*
South Africa (2002) <sup>9</sup>	PCR, serology for LGV	18	6.5	54	—*	3.2	64.5
China (2002) <sup>10</sup>	PCR	31	42	0	—*	—*	—*
The Netherlands (2001) <sup>11</sup>	PCR	48	3.3	0.9	—*	—*	—*
Senegal (2000) <sup>12</sup>	PCR	13	15	56	—*	—*	—*
India (1999) <sup>13</sup>	PCR	26	10	23	—*	—*	22.2
Madagascar (1999) <sup>14</sup>	PCR, clinical diagnosis for LGV	10	29	33	—*	8	—*
Jamaica (1999) <sup>15</sup>	PCR, clinical diagnosis for donovanosis and LGV	52	10.2	23.7	18.5	2.3	22
Thailand (1998) <sup>16</sup>	PCR	81.6	2.3	0	—*	—*	45.8
USA (1999) <sup>17</sup>	PCR	31	19	39	—*	—*	10

\*Disease not included in evaluation.

the virus is mediated by attachment of the viral envelope to the cell surface receptor (heparin sulfate). This fusion allows the de-enveloped virus capsid to be transported to the nuclear pores and release of viral DNA into the cell. The immediate early (IE) or alpha genes of the virus initiate the replication and then activate the early or beta genes. The beta gene produces enzymes necessary for viral replication, such as HSV thymidine kinase and the replication proteins. Gamma genes are the last to be expressed, and these genes code for structural proteins. Assembly of the herpes virus nucleocapsids begins in the nucleus. The replicative efficiency of HSV is poor, as the ratio of infectious to incomplete virions is low.

Once replication establishes inside the cell's nucleus, virus spreads to surrounding cells, damaging epidermal and dermal layers. The virus then enters peripheral sensory or autonomic nerve endings and migrates to the nerve root ganglia. Once in the ganglia the virus establishes a lifelong, latent infection from which periodic reactivation and replication occur. With reactivation, the virus descends from the ganglia and nerve root to the genital mucosa or skin. These reactivation processes classically cause genital ulcers, but asymptomatic reactivation is common.

## CLINICAL FEATURES

First episode of HSV infections occurs in those people without a previous history of genital herpes. The first episode may be primary, in which the affected person is seronegative for HSV antibodies, or it may be non-primary or first recognized recurrence in a person with serologic evidence of previous infection. A primary episode of HSV infection occurs after an incubation period of about 4 days, with a range of 2–12 days. Characteristically, the lesions arise

as multiple, painful, small, grouped vesicles on an erythematous base. These vesicles soon rupture to form erosions and shallow ulcers. The other features include edema of the external genitalia and tender, non-fluctuant inguinal lymphadenopathy. Without treatment the first episode lasts 3–4 weeks. Recurrent episodes are less severe and last 5–10 days only.

## DIAGNOSIS

In the majority of settings, the diagnosis of genital herpes is made clinically based on the characteristic grouped vesicles with an erythematous base. However, other conditions such as chancroid, syphilis, and contact dermatitis may present in a similar manner. Clinical diagnosis of genital herpes is poor even in experienced clinicians as was demonstrated in a study that showed that only about 40% of new genital herpes infections are diagnosed correctly on clinical suspicion.<sup>19</sup> Detection of HSV DNA from lesional samples by polymerase chain reaction is the most sensitive and specific method at present. Other methods include cell culture or antigen detection by immunofluorescence. Type-specific serologic tests for HSV 1 and HSV 2 may also be used, especially for patients from whom lesional samples cannot be obtained.

## TREATMENT

The recommended regimen for primary episode includes acyclovir, 400 mg three times a day or 200 mg five times a day for 7–10 days. Alternatively, famciclovir can be given in a dose of 250 mg three times a day or valacyclovir, 1 g twice daily for 7–10 days. Recurrent episodes can be treated with acyclovir in the

same doses as mentioned above, but only for 5 days. Alternate regimens include famciclovir in a dose of 125 mg two times a day for 5 days or valacyclovir 500 mg twice daily for 3–5 days.

## Syphilis

Although the incidence of syphilis has declined steadily for most of the twentieth century in Western Europe and North America, it is still an important infection in developing countries. The etiologic agent is a spirochete, *Treponema pallidum* (*T. pallidum*), a spiral structure visible by light microscopy only under dark-field illumination, and it cannot be grown on artificial growth media. In tissue culture and in animal models it divides slowly, with a replication time of approximately 30 hours. Transmission by sexual contact requires contact with moist mucosal or cutaneous lesions. *T. pallidum* cannot be distinguished in the laboratory from the agents responsible for yaws and pinta (*T. pertenue* and *T. carateum*, respectively). The organism is highly susceptible to drying.

## PATHOGENESIS

*T. pallidum* has not been shown to produce either exotoxins or endotoxins. Following experimental infection in the rabbit, *T. pallidum* begins to replicate once it has passed through the epithelium. An initial polymorphonuclear leukocyte response is soon replaced by an infiltrate of T and B lymphocytes. The primary chancre also contains mucoid material, mainly hyaluronic acid and chondroitin sulfate, which may modulate the host immune response. Secondary lesions appear in a certain proportion of infected persons some weeks after the primary infection. Much of the pathology of these secondary manifestations of syphilis may be immune complex mediated. High levels of antitreponemal antibody are present in the circulation, but cell-mediated immune responses are depressed. Without adequate treatment the organism can survive in the body for many years and may lead to tertiary syphilitic lesions characterized by the presence of a small number of organisms and a lymphocytic host response giving rise to endarteritis.

## CLINICAL FEATURES

After incubation period of 9–90 days (median 21 days), an ulcer, known as a chancre of primary syphilis, develops at the site of inoculation. Typically, the chancre is a single painless, indurated lesion with a raised edge. In men it is most commonly on glans penis, the foreskin, the coronal sulcus, or the shaft of the penis and in women on the cervix or vulva. The chancre does not bleed on contact. It is often accompanied by inguinal lymphadenopathy with the enlarged glands being characteristically firm, discrete, slippery, and painless. Without treatment the chancre characteristically resolves over 2–6 weeks. Secondary manifestations of syphilis appear generally between 3 and 6 weeks after the first appearance of the chancre. Secondary syphilis is usually recognized by the appearance of a non-itchy skin rash

that may be papular, macular or rarely pustular in nature. In moist areas of the body (e.g., perineum and axilla) the papules may become soft raised lesions known as condylomata lata. These lesions, teeming with spirochetes, are highly infectious. The rash may also be seen on the palms and soles. Mucous membranes may be involved with mucous patches or oral ulceration, sometimes in the form of the characteristic “snail track” ulcer. In addition to its cutaneous manifestations, secondary syphilis may cause systemic illness, giving rise to fever, malaise, generalized lymphadenopathy, nephritis, hepatitis, meningitis, or uveitis.

The lesions of primary and secondary syphilis generally resolve spontaneously after several weeks. If not treated, or inadequately treated, the patient then enters the latent stage of the disease and is likely to develop tertiary syphilis at some time in the future. The lesions of tertiary syphilis fall into three categories: the gumma, cardiovascular disease, and central nervous system disease. The classic Oslo study of untreated syphilis, in which some 1400 patients were followed up for up to 50 years, found that the most common late manifestation was the gumma, a painless “punched out” ulcer with little or no inflammatory reaction, which developed in 15% of the patients. Most of the lesions were cutaneous (about 70%) and 10% involved bone. Most cases occurred in the first 15 years following infection. Cardiovascular lesions (aortitis, aortic valve disease or coronary ostial occlusion) were seen in 15% of men and 8% of women, with onset typically 30–40 years after infection. Neurological manifestations were seen in 9% of men and 5% of women, with meningovascular disease typically occurring after 15–20 years and tabes dorsalis or general paresis after 20–30 years.<sup>20</sup> A detailed account of syphilis and its manifestations are given in a separate chapter.

## DIAGNOSIS

The most specific diagnostic method of early syphilis is identification of the spirochete under dark-field microscopy in exudate from the ulcer, condylomata lata or lymph node aspirate. Other direct diagnostic methods are direct fluorescent antibody test for *T. pallidum* (DFA-TP) or polymerase chain reaction (PCR). Serologic tests are used as indirect methods of diagnosing syphilis using non-treponemal tests such as the rapid plasma reagin test (RPR) or treponemal tests such as the fluorescent treponemal antibody absorption (FTA-ABS) test, the *T. pallidum* passive particle agglutination assay (TP-PA) or the *T. pallidum* hemagglutination assay (TPHA). More recently, a number of immunochromatographic strip tests have been developed as rapid point-of-care tests for syphilis screening using either serum or whole blood.

## TREATMENT

Penicillin remains the mainstay of treatment for syphilis since confirmation of its effectiveness in 1943. There have been no reports of *T. pallidum* developing resistance against penicillin. Single intramuscular injection of 2.4 million (1.2 million in each buttock) units of benzathine penicillin is the treatment of



choice. In patients allergic to penicillin, desensitisation should be attempted. If that is not possible, alternative treatment regimens like doxycycline 100 mg twice daily, or erythromycin 500 mg four times daily, for 2 weeks for early syphilis and for 1 month in cases of late syphilis can be given.

## Chancroid

Chancroid is caused by the bacterium *Haemophilus ducreyi*, a small facultative anaerobic gram-negative bacillus, endemic in settings with poor access to health services such as Africa, Asia and South America, and the Caribbean. Although generally rare in industrialized countries, there have been several well-documented outbreaks in North America since the 1970s. Characteristic features of these outbreaks have been a high male-to-female case ratio, the involvement of sex workers and the low socioeconomic status of the populations affected. A study in Nairobi investigated the role of asymptomatic females in the transmission of the disease and concluded that they were of little importance.<sup>21</sup> Studies among Australian soldiers during the Vietnam war suggest that chancroid is more common among uncircumcised than circumcised men.<sup>22</sup> In the era of the human immunodeficiency virus (HIV) and AIDS, chancroid is of particular importance as prospective studies among both males and females at high risk of HIV infection have suggested that it significantly increases the risk of transmission of HIV via heterosexual contact, by increasing infectivity, susceptibility or both.<sup>23,24</sup>

## PATHOGENESIS

Histopathologically, chancroid ulcers contain three distinct zones, namely, a superficial zone of necrotic tissue, fibrin and numerous bacteria, an intermediate edematous zone with new vessel formation, and a deep zone of dense infiltrate of neutrophils and plasma cells with fibroblastic proliferation. The inguinal lymphadenopathy is paucibacillary but with a large number of neutrophils.

## CLINICAL FEATURES

After infection, a papule appears at the site of infection after about 3 days, with an incubation period that ranges from 1 to 7 days. The papule quickly ulcerates giving rise to the typical painful, soft ulcer of chancroid. Characteristically, the ulcer has a purulent base with an undermined edge and bleeds on contact. Presentation with multiple ulcers is common. Unilateral, but sometimes bilateral, painful inguinal lymphadenopathic swellings (bubo) are seen in about 30–50% of cases. Atypical presentations are, however, common, and even in experienced hands chancroid cannot reliably be distinguished from primary syphilis on clinical grounds.<sup>25</sup> Herpes simplex virus infection, LGV, and donovanosis also come into the differential diagnosis of chancroid. Chancroid may cause rapid, extensive local destruction of the genitals, particularly in HIV-infected individuals.

## DIAGNOSIS

Gram-stained smears obtained from ulcers lack both sensitivity and specificity for the diagnosis of chancroid. Isolation of *H. ducreyi* from the ulcer provides a definitive diagnosis, but this is a laborious process. To obtain adequate material, swabs should be taken from the ulcer base (invasive and extremely uncomfortable for the patient) and plated directly on appropriate blood-containing media enriched with fetal calf serum and Vitox and made selective with vancomycin. For optimal rates of isolation, media made up from both GC agar and Mueller–Hinton agar base should be inoculated. Plates should be incubated for at least 72 hours in an atmosphere of 5% carbon dioxide at 33°C. This requires both high-quality laboratory equipment and highly trained staff.

## TREATMENT

Chancroid ulcers should be kept clean and dry with regular washing with soap and water. For a number of years, sulfamethoxazole-trimethoprim (cotrimoxazole) or erythromycin in standard dosage given by mouth for 7 days have been the effective therapy, but *H. ducreyi* isolates have acquired plasmid-mediated resistance to sulfonamides. Since hardly any studies have been conducted recently, the current prevalence and distribution of anti-microbial resistance in *H. ducreyi* is not known, but macrolides, quinolones, and cephalosporins, such as ceftriaxone are still effective against *H. ducreyi*. Ciprofloxacin, 500 mg daily for 3 days by mouth, ceftriaxone, 250 mg as a single intramuscular dose or azithromycin 1 g orally in a single dose appear to be effective treatment regimens.

## Lymphogranuloma Venereum

The epidemiology of lymphogranuloma venereum (LGV) is not well-defined because of lack of a sensitive and specific diagnostic test for its detection. LGV is largely confined to the tropics and in most places it accounts for only a small proportion of patients with STIs. The disease is seen more often in men than women, though the late anorectal complications are more prevalent in women.

## ETIOLOGY AND PATHOGENESIS

Lymphogranuloma venereum is caused by the invasive L1, L2, and L3 strains of *Chlamydia trachomatis*. Characteristically, the pathological features are a transient, herpetiform primary ulcer of the external genitalia. In many cases, however, the primary lesion is not noticed by the patient on account of lack of symptoms or being internal on the cervix in women. Most patients seek healthcare when the lymphatic system becomes infected. Such infections eventually lead to thrombolympangitis and perilymphangitis with proliferation of the endothelial cells of the lymphatics. In the lymph nodes, prominent migration of neutrophils leads to characteristic abscess formation seen in the inguinal and femoral glands.

## CLINICAL FEATURES

The small ulcer of LGV is so evanescent that most patients miss it. However, in men who have sex with men genital ulceration and inguinal syndrome may be present at the same time.<sup>26</sup> Patients usually present at the “bubo” stage. Thus, when a sexually active adult presents with an inguinal bubo not associated with genital ulcer, LGV should be suspected. The incubation period ranges from 3 to 30 days. If recognized the presentation is typically a small, self-limiting, painless ulcer on the genitalia. The second phase of the illness is the development of increasingly painful lymphangitis and lymphadenitis, accompanied by fever and malaise. The infected nodes (bilateral in one third of cases) coalesce into a matted mass. The nodes may rupture and open into multiple sinuses. Untreated, the disease may cause extensive lymphatic damage resulting in elephantiasis of the genitalia. The combination of elephantiasis with skin breakdown sometimes seen in late cases is referred to as esthiomène. In women and in men having sex with men, the disease may present as an acute proctocolitis which, in a proportion of cases, leads to abscess formation, fistulae, and rectal strictures. In the Caribbean, a high incidence of vulval carcinoma has been recorded among premenopausal women with scars of either LGV or donovanosis.<sup>27</sup>

## DIAGNOSIS

At primary health-care level, the diagnosis is mostly based on clinical examination. The diagnosis of LGV can only be confirmed in specialist centres with facilities for the isolation and identification of *C. trachomatis* L1–3 strains, or the ability to perform the micro-immunofluorescence serological test.<sup>28</sup> Other serological tests show cross-reaction with other serovars of *C. trachomatis*, and with other species of Chlamydia, such as *C. pneumoniae*. The accepted criterion for a positive diagnosis is a micro-immunofluorescence titer of 1:512. The presence of stellate abscesses in biopsy material is suggestive of LGV. Direct fluorescent antibody (DFA) staining may be used to demonstrate chlamydial elementary bodies in tissue or discharge from buboes. The process to obtain an accurate diagnosis, much as in the case of diagnosis of chancroid, is costly.

## TREATMENT

Being an infection caused by one of the chlamydia group, tetracyclines and erythromycin are effective treatments. If treatment is delayed, antibiotics are of little benefit in preventing the late sequelae of rectal stricture and elephantiasis of the genitalia. Corrective surgical procedures may be of benefit in cases with extensive elephantiasis or deformity. Any suspicious areas in healed scars should be examined for malignant change.

## Donovanosis

Donovanosis is caused by a bacterium, endemic in areas localized to a few specific parts of the tropics. The most important of these are currently the southeast India, Papua New Guinea (PNG),

Brazil, The Guyanas, and eastern parts of South Africa. The disease is strongly associated with sex work and low socioeconomic status. Outside PNG, the highest recently reported incidence of donovanosis has been in Durban, South Africa, where 16% of genital ulcers in men were due to donovanosis.<sup>29</sup>

## ETIOLOGY AND PATHOGENESIS

The disease is caused by an intracellular, encapsulated gram-negative coccobacillus, previously called *Calymmatobacterium granulomatis*. Recently the organism has been re-classified as a *Klebsiella* on the basis of ribosomal RNA sequences.<sup>30</sup> The disease primarily attacks the skin and the bacteria are carried to inguinal nodes where they occasionally cause a suppurating periadenitis (“pseudobubo”) but mostly these lesions are independent of the lymph nodes. The key histological features are epithelial hyperplasia, a dense dermal infiltrate of plasma cells and scattered large macrophages containing clusters of Donovan bodies.

## CLINICAL FEATURES

The first manifestation, appearing after 3–40 days incubation period, is usually a small papule which ruptures to form a granulomatous lesion that is characteristically pain-free, “beefy-red” in color, bleeds readily on contact and is often elevated above the level of the surrounding skin. If not treated, the ulcers gradually extend along skin folds towards the groins and the anal area. Complications include rapid extension of lesions secondarily infected with fusospirochaetal organisms, scarring, elephantiasis, and rarely the development of squamous carcinoma.

## DIAGNOSIS

The diagnosis requires the demonstration of intracellular Donovan bodies in biopsy material or smears taken from active areas and stained by Giemsa or Leishman stains.

## TREATMENT

The most widely used antibiotics are tetracyclines, chloramphenicol, cotrimoxazole, and erythromycin. Thiamphenicol, lincomycin, norfloxacin, and azithromycin have recently been shown to be of value, but studies in Australia have shown that azithromycin is the treatment of choice.<sup>31</sup> Treatment should be continued until lesions have resolved and, if possible, a little longer to reduce the risk of relapse. Corrective surgical procedures are required in some patients to ameliorate deformities from scarring. Treatment of sexual partners who do not have lesions is not thought necessary.

## Non-venereal Causes of Genital Ulcer

Non-venereal ulcers in men and women are commonly seen in genitourinary clinics. Genitalia may be traumatized and develop minor erosions and ulcerations even during normal sexual activity, more often with sexual aids (sexual toys), the practice of dry sex or vigorous sex under the influence of drugs.

In research settings, 12–50% of genital ulcers have no defined etiology, even with modern molecular diagnostic methods.<sup>8,14,15</sup>

Many dermatological or systemic and blistering disorders can cause ulceration of the genitalia in both sexes. In a descriptive, observational study conducted in Brazil in 2005 among women approximately 55% of the ulcers were due to a sexually transmitted pathogen, predominantly herpes simplex virus (53%) and about 2% were syphilitic ulcers. In the remaining 45% of the cases, the ulcers were non-sexually transmitted. Some of the identified causes of the latter were Behçet disease, hidradenitis suppurativa, ulcerative lichen sclerosis simplex, pemphigus vulgaris and vulvar intra-epithelial neoplasia (VIN) and autoimmune ulcers.<sup>32</sup> In a small study of 13 immunocompetent, non-sexually active adolescent girls in Paris, acute GUD was related to infection with the Epstein-Barr virus in 4 patients (31%), Behçet disease in 1 patient and no pathogen was identified in the rest (about 42%).<sup>33</sup>

Whatever the cause of an ulcer, it is important to be aware that the presence of an ulcer increases the risk of acquiring or transmitting HIV. Therefore, due attention and early management are essential. Some of the uncommon non-sexually related causes of GUDs are described below.

**Amoebiasis**, caused by the pathogen *Entamoeba histolytica*, is typically a disease of the colon. This is endemic in many tropical countries. Cutaneous amoebiasis may involve the genitalia.<sup>34</sup> It manifests as a well-defined, serpiginous, tender ulcer with indurated, erythematous margins. The base of the ulcer is friable and bleeds easily. There is a foul-smelling hemopurulent discharge. Regional lymph nodes are often enlarged. The ulcer may mimic syphilitic chancre, chancroid, donovanosis, and genital neoplasia. Diagnosis can be made by wet mount to visualize the parasite. Stool examination may add to the diagnosis. Treatment includes metronidazole, 400 mg three times daily for 10 days or tinidazole, 2 g once a day for 2 days.

**Behçet disease** is characterized by a triad consisting of oral aphthous ulcers, genital ulcers, and uveitis. Genital lesions begin as small asymptomatic papules or papulovesicles, which soon erode to form erythematous, painful, punched out ulcerations. The ulcers heal spontaneously over a period of time (several weeks to months), but may recur. The diagnosis is based on the presence of oral aphthae and involvement of other organ systems including the eye. Genital lesions may mimic syphilitic chancre, genital herpes, chancroid, and sometimes, when lesions are destructive, donovanosis. Extensive ulcerations should be treated with colchicine (0.5 mg three times a day), dapsone (100–200 mg/day), prednisolone (40 mg/day) or once weekly methotrexate.

**Crohn disease** is a chronic, inflammatory, granulomatous disease that primarily affects the gastrointestinal tract. Cutaneous extension of the bowel disease affects perianal and genital skin. Alternatively, metastatic Crohn disease may affect distant sites including perianal, vulval, penile, or scrotal skin. The skin lesions caused by local extension may be in the form of nodules, abscesses, sinus tracts, and fistulae. The metastatic disease is characterized by deep, punched out ulcers. The diagnosis can be confirmed by

histopathological examination of a tissue biopsy. Non-caseating granuloma in the dermis or subcutis along with epidermal erosion is characteristic. Cutaneous lesions may resolve after bowel disease improves. Treatment for Crohn disease should be done in consultation with a gastroenterologist.

**Human bites** to the genitalia are one of the rare causes of penile ulceration. Although patients tend to present late due to embarrassment, such traumatic injuries are increasingly being reported, probably due to the increasing frequency of orogenital sex. The ulcers are often contaminated with oral flora and they should be treated early with irrigation and debridement. Bite wounds to the genitalia may result in superficial tissue necrosis and deep ulceration due to the virulent human oral flora. Anti-microbial treatment is indicated provided malignant lesions have been excluded.<sup>35,36</sup> The role of prophylactic antibiotics is not clearly defined in animal bites, but there is evidence that prophylactic anti-microbial treatment is of benefit following human bites, but the data are insufficient, particularly for the genital area.<sup>37</sup>

**Fixed drug eruptions** frequently affect the glans penis and may present as genital ulcer.<sup>38</sup> A history of recent drug intake may help in the diagnosis.

## Syndromic Management of GUD

Although the literature may describe clinical appearances that are supposed to assist towards identification of causative agents for particular ulcers, practice in the field has shown that even experienced physicians make the wrong diagnosis from that. A number of laboratory diagnostic tests, which may help in the confirmation of the diagnosis of genital ulcers exist, and some are mentioned in Table 53.2. However, high-quality laboratory facilities are not available in many health-care settings and at nearly all primary health-care facilities. Therefore, depending on the relative prevalence of causative organisms for GUD and their antibiotic sensitivities, appropriate treatment combinations should be given syndromically using combinations suggested in Table 53.3. The guiding principle is shown in Fig. 53.1.

The decision to treat for any combination of the above will depend on the local epidemiology of the infections and the national treatment guidelines for sexually transmitted infections. All fluctuant buboes should be aspirated, not surgically incised, directing a large bore needle through as much normal skin as possible. Burst buboes should be cleaned and dressed with antiseptic solution or dilute saline solution until epithelialization is complete.

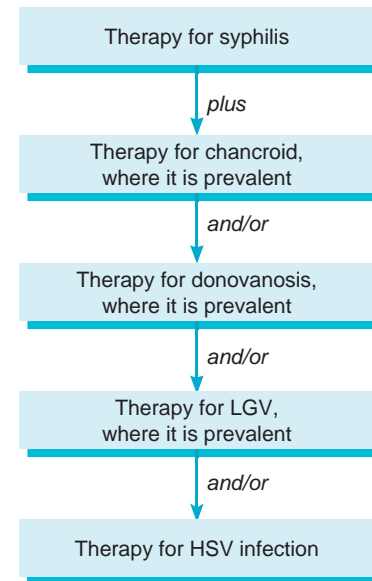
Surveillance for genital herpes should be observed in all settings as the HSV 2 seems to be predominating as the cause of GUD in both developing and developed countries.<sup>39–41</sup> Recent reports from parts of Africa, Asia, and Latin America indicate that GUD is more frequently a result of HSV 2 infections. In order to minimize overtreatment in Peru, where HSV caused 43% of genital ulcers, patients with vesicular genital lesions were excluded in syndromic management of GUD. This reduced the over-treatment rate for syphilis and chancroid from 76% to 58%, but the sensitivity for these two diseases was also reduced



**Table 53.2:** The Appropriate Specimens and Diagnostic Tests for Sexually Transmitted Microorganisms Causing Genital Ulcer-Adenopathy Syndrome

Microorganisms	Diseases	Laboratory tests	Specimens
Herpes simplex virus	Genital herpes	Tzanck smear from ulcer/vesicle	Ulcer base smear
		Cell culture, Antigen detection	Ulcer swab
		DNA tests (PCR)	Ulcer swab
		Type-specific serology	Blood
<i>T. pallidum</i>	Syphilis	Dark-field microscopy, Serology	Fluid from ulcer, Blood
<i>H. ducreyi</i>	Chancroid	Gram-stain, Culture, PCR	Ulcer swab
<i>Klebsiella granulomatis</i>	Donovanosis	Direct stain/Wright-Giemsa, Culture, PCR	Tissue biopsy
<i>C. trachomatis</i>	LGV	Cell culture, Antigen detection, PCR	Ulcer swab

from 100% to 88%.<sup>42</sup> If specific antiviral treatment of HSV 2 is not considered it will have implications on the efficacy of the syndromic management of GUD. In areas of high HIV prevalence, the clinical presentation of ulcers caused by HSV 2 is different from the classical descriptions. In such areas the management for suspected genital herpes should include specific antiviral therapy, such as acyclovir, famciclovir or valacyclovir. The GUD flowchart (Fig. 53.1) introduced by WHO in their

**Fig. 53.1:** Recommended syndromic treatment for genital ulcer disease.

revised guidelines proposes specific treatment for HSV 2 in the first-line treatment combinations for GUD.<sup>43</sup>

### EFFICACY OF SYNDROMIC MANAGEMENT FOR GENITAL ULCER-ADENOPATHY SYNDROME

A recent review showed sensitivity for the algorithm for the diagnosis and treatment of GUD in men ranging from 68% to 98%.<sup>44</sup> In China, in patients with genital ulcers, the sensitivities were 78.3% and 75.8%, specificities were 83.6% and 42.9%, and positive predictive values were 60.0% and 41.0% for the diagnosis of syphilis and genital herpes, respectively, using the syndromic

**Table 53.3:** Treatment Options that can be Combined for the Syndromic Management of GUD

Genital herpes (first episode)	Genital herpes (recurrent episode)	Syphilis	Chancroid	Donovanosis	LGV
Acyclovir, 400 mg three times a day for 7–10 days	Acyclovir, 400 mg three times a day for 5 days	Benzathine penicillin, 2.4 million units IM at a single session	Ciprofloxacin, 500 mg orally, twice daily for 3 days	Azithromycin 1 g orally on first day, then 500 mg orally once a day until lesions heal	Doxycycline, 100 mg orally, twice daily for 14 days
Acyclovir, 200 mg five times a day for 7–10 days	Acyclovir, 200 mg five times a day for 5 days	Procaine benzylpenicillin, 1.2 million units IM daily for 10 consecutive days	Erythromycin, 500 mg orally, three times daily for 7 days	Doxycycline, 100 mg orally, twice daily until lesions heal	Erythromycin, 500 mg orally, four times daily for 14 days
Famciclovir, 250 mg three times a day for 7–10 days	Famciclovir, 125 mg twice daily for 5 days	Doxycycline, 100 mg orally twice daily for 14 days	Azithromycin, 1 g orally as a single dose	Erythromycin, 500 mg orally, four times daily until lesions heal	
Valacyclovir, 1g orally twice a day for 7–10 days	Valacyclovir, 500 mg orally twice a day for 3–5 days		Ceftriaxone, 250 mg IM, as a single dose		

approach.<sup>45</sup> In a recent study from Taiwan, syndromic management was found to be a more cost effective protocol compared with the current and etiologic protocols for the management of STIs.<sup>46</sup> A study from Nigeria concluded that syndromic case management of STIs can be conveniently integrated into primary healthcare delivery system.<sup>47</sup> The syndromic approach, though simple and effective at a considerably reduced cost, has some limitations. Many patients do not fit into the pattern of a classical syndrome even when symptoms related to genitalia are present as has been brought out in a large study from central India.<sup>48</sup> However, in the majority of cases, the syndromic management protocol for genital ulcer adenopathy syndrome provide adequate treatment to more than 90% of patients with GUD; however, this is at the cost of overtreatment in a significant proportion of patients.

It should be remembered that whether a country adopts the syndromic approach or the laboratory-based etiologic approach, asymptomatic patients who remain out of the ambit of either a syndrome or a symptomatic infection will need supplementary strategies for the detection of infection. Such strategies include screening and case finding policies.

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# Urethral Discharge

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## Introduction

Sexually transmitted infections (STIs) are caused by over 30 diverse pathogens, including bacteria, viruses, protozoal agents, fungal agents, and ectoparasites. Most STI pathogens infect the reproductive tract as their primary site. *Neisseria gonorrhoeae* (*N. gonorrhoeae*) and *Chlamydia trachomatis* (*C. trachomatis*) are the two most common sexually transmitted bacteria and commonly present with urethral discharge in men.

## Causative Pathogens and Pathogenesis

The causes of urethral discharge are classified as gonococcal and non-gonococcal. The former is the most common cause of acute urethral discharge in the African region and the south-east Asia region, whereas chlamydial infections seem to predominate in other geographic areas, particularly in Europe and North America. For example, data from men with urethral discharge attending STI clinics in Africa show the causative agent to be *N. gonorrhoeae* in more than 50% of cases and *C. trachomatis* is implicated in a range of 5–15% of cases, and dual infections are common.<sup>1,2</sup> Non-specific urethritis (NSU), after exclusion of cases of *N. gonorrhoeae* and *C. trachomatis*, accounts for about one-quarter or one-third of cases of urethral discharge. In settings where it has been investigated, *Trichomonas vaginalis* is not an infrequent pathogen, accounting for perhaps 2–20% of cases of acute urethral discharge.<sup>3</sup> Other organisms such as *Mycoplasma genitalium* and *Ureaplasma urealyticum* have been implicated, but they are difficult to demonstrate. *Candida* species can be isolated from patients with urethritis in less than 1% of cases; however, its significance is not fully understood. *Candida* urethritis is often associated with balanitis. Other rare causes include Meningococcus, group B streptococci, *Staphylococcus saprophyticus*, *Gardnerella vaginalis*, and *Corynebacterium genitalium*.

### GNOCOCCAL INFECTION

*N. gonorrhoeae*, a gram-negative diplococcus found only in humans, is especially adept at colonizing the epithelial surfaces

of the male and female urogenital tract, conjunctiva, pharynx, rectum, and synovium. Its virulence is conferred by the presence of pili that mediate adherence sufficient to withstand hydrodynamic forces within the urethra. These pili also inhibit uptake by phagocytes. No specific toxins have been described as being produced by *N. gonorrhoeae*, but the organism is highly adept at avoiding the host immune response. The pilus antigens, the protein designated as P.II, and the lipo-oligosaccharide are capable of antigenic variation sufficient to permit repeated re-infection of the same host within a short period. The mucosal immune response to infection is characterized by the production of IgA, IgM, and IgE which can inhibit adherence and facilitates opsonization, but the bacteria produce an IgA1 protease which may impair the host mucosal immune response.

The risk of contracting gonorrhea after a single exposure is about 20% for males and probably higher for females. Most men develop symptoms within 5 days of infection, with an average incubation period of 3 days. Ninety percent of men will experience symptoms within 14 days of infection. Asymptomatic infections are more frequent in women, accounting for up to 80% of infections detected in sexual partners of symptomatic patients.

### Clinical Presentation

Gonococcal infections are commonly limited to mucosal surfaces, such as the urethra, the cervix, rectum, pharynx, and conjunctiva. The prepubertal vaginal epithelium is also susceptible to infection as the vaginal epithelium will not have keratinized in young adolescent girls. Symptomatic uncomplicated gonococcal infections in men manifest typically as thick, yellow urethral discharge (Fig. 54.1). Accompanying symptoms may include metal itching, burning, dysuria, and frequency of micturition. Infections of the pharynx and rectum (mostly asymptomatic) can result from orogenital and genitoanal sexual contact in men who have sex with men, as well as in women practicing anal sex. Women can also experience rectal infection by contamination from an infected vaginal discharge.



**Fig. 54.1:** Thick, yellow urethral discharge typically seen in symptomatic uncomplicated gonococcal infection.

## Complications

In men, spread of the infection to the epididymis, usually unilateral, is the most common complication. Acute epididymitis, which occurs in up to 20% of untreated infection, has to be distinguished from acute testicular torsion, which is a surgical emergency. Certain complications of gonorrhea are now seldom encountered in industrialized countries but may still be seen in developing countries. These include abscess and fistula formation resulting from spread of infection to various glands associated with the genitourinary tract, such as the prostate gland, Tyson, Littre, and Cowper glands. Ultimately, these may lead to urethral stricture, a complication difficult to manage, which appears to show marked geographical variation in settings with poor access to health-care services.<sup>4,5</sup> In women, untreated cervical infection may lead to involvement of the pelvic organs including the endometrium, the fallopian tubes, and the pelvic peritoneum, resulting in the syndrome of pelvic inflammatory disease.

## Disseminated Infection

In approximately 2% of patients with gonorrhea, disseminated gonococcal infection may arise, usually originating from asymptomatic infection. It manifests most often as an asymmetric oligoarthritis with a predilection for knees, ankles, and large and small joints of the upper limb.

Tenosynovitis occurs frequently. On the skin lesions may be seen presenting classically as tender necrotic pustules. Gonococcal arthritis accounts for as much as 20% of acute arthritis in young adults in the tropics.<sup>6</sup> Rarer manifestations of disseminated gonococcal infection include endocarditis and meningitis. Disseminated infections can no longer be expected to respond to penicillin as in the past.

## Ocular Gonococcal Infections

Ocular gonococcal infection in adults, which is presumed to follow autoinoculation with a contaminated finger in most cases, is a common and potentially blinding complication in developing countries. It presents as an acute purulent conjunctivitis, which may progress rapidly to corneal perforation in the absence of adequate systemic antimicrobial treatment.

## Laboratory Diagnosis

The definitive diagnosis of gonorrhea rests on the isolation of *N. gonorrhoeae*. The demonstration of gram-negative, intracellular diplococci in urethral smears has sensitivity and specificity of over 95% for the diagnosis of gonorrhea in men, but both sensitivity and specificity are considerably lower in women. In disseminated infection, specimens from joints, blood or skin lesions give a rather poor yield and the organism may be isolated more readily from the genital tract. When cultures are to be made, the sites for swabbing should be determined by the history and examination findings. In men, it is good to obtain a urethral specimen by insertion and rotation of a swab in the urethra for 5 seconds.

For women, the ectocervix should be wiped clean and a swab should be inserted into the cervical os and rotated for 10 seconds. Rectal swabs are best obtained through a proctoscope. *N. gonorrhoeae* is a delicate organism, highly susceptible to drying, and prompt inoculation of media and careful adherence to recommended laboratory techniques is important to maximize isolation rates. Newer techniques for gonococcal detection are the molecular methods using nucleic acid amplification tests (NAATs). Although the use of molecular methods has increased in the last few years, culture remains important for the determination and monitoring of antimicrobial resistance in *N. gonorrhoeae*.

## Treatment

A large proportion of isolates of *N. gonorrhoeae* is now resistant to penicillins, tetracyclines, and quinolones. The most effective and recommended class of antibiotics is the third-generation cephalosporins with careful monitoring as treatment failures have been reported recently with the oral third-generation cephalosporins. Ideally, treatment should provide us a single dose of oral regimen to improve compliance, but with the recent emergence of highly resistant strains, parenteral therapy is becoming more the preferred route of administration to maintain high cure rates. The dose administered should give a serum level of at least three times the minimum inhibitory concentration for 8 or more hours.

The current World Health Organization (WHO) treatment recommendations for uncomplicated gonorrhea are ceftriaxone 250 mg intramuscularly as a single dose, or cefixime 400 mg orally as a single dose. Where available, spectinomycin 2 g by intramuscular injection, as a single dose, can be used as an alternative. Treatment of sexual partners should extend to all individuals exposed within 2 weeks of the onset of symptoms in the index patient. In the case of asymptomatic infection, all sexual partners within 4 weeks of diagnosis should be offered treatment. Some authorities recommend that all sexual partners within the previous 3 months should be screened and treated. If the syndromic approach to diagnosis and treatment is being pursued, combined treatment for both gonorrhea and chlamydial infection should be given to all patients with urethral discharge.

## CHLAMYDIAL INFECTIONS

The demonstration in 1909 of chlamydial inclusions in cervical scrapings from the mother of an infant with inclusion conjunctivitis and in urethral scrapings from her male partner laid the basis for our understanding of genital chlamydial infections, but it was not until it became possible to isolate *Chlamydia trachomatis* (*C. trachomatis*) in tissue culture in 1965 that the extent of the morbidity due to this organism became clear.

## Causative Pathogens and Pathogenesis

*C. trachomatis* is the most prevalent sexually transmitted bacterial pathogen in industrialized countries, and appears to be at least equally prevalent in developing countries.<sup>7</sup> Studies in industrialized countries and some parts of Africa have shown that genital chlamydial infection is more prevalent in younger age groups, even after taking differences in sexual activity into account, implying that some degree of protective immunity may develop after natural infection. *C. trachomatis* is a gram-negative bacterium, which is an obligate parasite of eucaryotic cells. The genus *Chlamydia* has a unique life cycle. The metabolically inert infectious elementary body has a rigid cell wall and is adapted for extracellular survival. It preferentially attacks columnar epithelial cells. After entering the host cell, it differentiates over a number of hours to the metabolically active reticulate body, which divides by binary fission until an intracellular inclusion is formed. The life cycle is completed when reticulate bodies condense to form elementary bodies, which are released from the inclusion after lysis of the host cell. A number of serotypes of *C. trachomatis* have been identified by the microimmunofluorescence test. Serotypes A to C cause ocular infection in trachoma endemic areas, whereas serotypes D to K cause genital tract infections worldwide. Serotypes L1, L2, and L3 are more invasive both *in vitro* and *in vivo*, and cause lymphogranuloma venereum (LGV). The pathological hallmarks of infection with *C. trachomatis* are: (i) the sub-epithelial lymphoid follicle, and (ii) fibrosis and scarring. The latter may progress for months and years even in the absence of chlamydial organisms demonstrable by conventional means. The host immune system is believed to play an important part in the pathogenesis of chlamydial infections.

## Clinical Presentation

The clinical spectrum of disease due to chlamydial infection is similar to that seen in gonococcal infection. Men present with urethritis, giving rise to urethral discharge that can be indistinguishable from that seen with gonococcal infection. However, characteristically chlamydial infections present with scanty discharge. In a proportion of cases, epididymo-orchitis may ensue. It is possible that urethral stricture is a late sequela of chlamydial urethritis.

## Diagnosis

The advent and introduction of NAATs have made it possible to expand testing for chlamydial infections, using non-invasive

**Table 54.1:** Treatment Combination Options for Urethral Discharge Syndrome

Condition	First line	Second line
Treatment options for gonorrhea	Ceftriaxone 250 mg intramuscularly, single dose Or Cefixime 400 mg orally, single dose	Spectinomycin 2 g IM as a single dose (in pregnant or penicillin-allergic patients) Or Gentamicin <sup>†</sup> 240 mg IM single dose
Treatment options for Chlamydia	Azithromycin 1 g single oral dose Or Doxycycline 100 mg twice daily for 7 days	

<sup>†</sup>Note that clinical efficacy has been documented for urethral gonococcal treatment, but there is limited data correlating laboratory minimal inhibitory concentrations (MICs) with clinical observations.

methods and samples, such as first catch urine and vaginal swabs. Where affordable, the use of NAATs is preferable for the diagnosis of chlamydial infections. Although NAATs are more sensitive than antigen detection tests or isolation, they remain expensive and require good laboratory facilities.<sup>8</sup> Serology has no place in the diagnosis of uncomplicated chlamydial infections with the exception of the more invasive LGV. Serology, however, is the method of choice for the diagnosis of neonatal chlamydial pneumonia. Reasons for this are that it is only possible to distinguish between antibodies to the various species of *Chlamydia* by the micro-immunofluorescence test, which is subjective and labor intensive. Other serological tests may give false positive results due to infection with the highly prevalent respiratory tract pathogen, e.g., *Chlamydia pneumoniae*.

## Treatment

*C. trachomatis* remains sensitive to tetracyclines and erythromycin, and single dose treatment with azithromycin is effective in uncomplicated chlamydial infection.<sup>9</sup> Table 54.1 gives a summary of current treatment recommendations for urethral discharge syndrome which combines the treatment of gonococcal infections and chlamydial infections.

## TRICHOMONIASIS

Trichomoniasis is caused by the flagellated protozoal parasite *Trichomonas vaginalis* (*T. vaginalis*). When viewed under the microscope on a wet mount, a viable organism can be recognized easily by the lashing movements of its flagella. *T. vaginalis* is the single most common curable STI worldwide, with an estimated 248 million cases occurring annually.<sup>10</sup> *T. vaginalis* has been isolated in 1–15% of cases of non-gonococcal urethritis in men. Recent community-based studies in East Africa have found prevalences of around 10% among truck drivers in Mombasa<sup>11</sup> and rural men in Tanzania.<sup>12</sup> Sexual contact is the usual mode of infection, but the parasite is known to survive on inanimate objects providing moist conditions; thus, fomites may occasionally



play a role in transmission. In women, the parasite attaches to the vaginal mucosa and competes nutritionally with the protective vaginal lactobacilli. This results in disappearance or diminution in number of lactic acid producing lactobacilli and leads to a corresponding rise in pH (4.5 and above) of the vaginal milieu. There is an inflammatory response with polymorphonuclear leukocytosis.

## Clinical Features

In men the infection is commonly asymptomatic. When symptomatic, probably in about 50% of cases, the most common presentation is with urethral discharge and, sometimes, dysuria.

## Diagnosis

Commonly, diagnosis is either by direct microscopy of a wet-mount preparation or culture using Diamond medium. However, *T. vaginalis* is difficult to demonstrate in male patients, and culture of a centrifuged first catch urine specimen may be the most sensitive method of a definitive diagnosis. NAATs offer the most sensitive diagnostic option, but they remain expensive and require good laboratory practice.

## Treatment

Metronidazole has been the mainstay of treatment for infection with *T. vaginalis*.

## MYCOPLASMA AND UREAPLASMA INFECTIONS

*Mollicutes* are a class of organisms that have developed from anaerobic bacteria by gene deletion. The genera *Mycoplasma*, *Ureaplasma*, *Acholeplasma*, *Anaeroplasm*, and *Asteroleplasma* make up more than 120 species, generally referred to as mycoplasmas. Of some 16 mycoplasmas detected in the human species, six appear to have the genitourinary tract as their primary site of colonization. These are *M. hominis*, *M. primatum*, *M. genitalium*, *M. spermatophilum*, *M. penetrans*, and *U. urealyticum*. Although infants may become colonized with genital mycoplasmas during birth, colonization after puberty occurs primarily as a result of sexual contact.<sup>13</sup> *M. genitalium*, as a new pathogen among the mycoplasmas, was first isolated in cultures of urethral discharge from men with non-gonococcal urethritis in the early 1980s and subsequently reported as a possible pathogen in male urogenital infections.<sup>14,15</sup> A number of studies have since implicated the mycoplasmas in the etiology of non-gonococcal urethritis, including studies in which investigators inoculated themselves intraurethrally with ureaplasma strains.<sup>16</sup>

## Clinical Features

The clinical features of *Mycoplasma* infection are similar to those caused by chlamydial infection. The urethral discharge may be significant or scanty and mucoid.

## Diagnosis

The detection of *Mycoplasma* and *Ureaplasma* in the male genitourinary tract can be done by collecting and testing a urethral swab specimen and/or a first-catch urine specimen by culture. However, *M. genitalium* is too fastidious to culture and antigen detection has not had great success in identifying the organism. The best results are obtained by using the polymerase chain reaction (PCR) technique.

## Treatment

Since diagnostic facilities for these organisms are not readily available, especially in resource-limited settings, management should depend being aware of clinical conditions in which *Mycoplasma* may be implicated. Accumulated evidence suggests that *C. trachomatis*, *M. genitalium*, and occasionally *Ureaplasma* are causes of non-gonococcal urethritis. The usual treatment of non-gonococcal urethritis with either tetracyclines or erythromycin is effective.

## Management of Urethral Discharge Syndrome

Early diagnosis and effective treatment of STIs are essential components of STI control programs. The traditional method for STI diagnosis has been through laboratory diagnosis of the etiological agent as outlined above. This is still the method of choice in many parts of the industrialized world. However, as can be inferred from the diagnostic procedures and requirements above, this approach is too expensive for most resource-constrained countries in terms of diagnostics, infrastructure, manpower, and maintenance. Additionally, it often results in delays in diagnosis and treatment and, in the case of urethral discharge, may miss the presence of mixed infections.

To address the limitations of laboratory-based etiological diagnosis, the WHO developed and advocated the use of treatment algorithms for a syndromic approach. The syndromic management of STI has advantages which include provision of care without delay, cost savings by not using expensive laboratory tests, treatment at first visit at the first port of call for the patient, and patient satisfaction. Management is simplified by the use of clinical flowcharts and allows time in the consultation to provide simple education messages, discuss partner notification and promote condoms. Antimicrobial therapy is provided at once to cover the majority of pathogens presumed responsible for that syndrome, in that specific geographical area. In the syndromic management, all male patients complaining of urethral discharge should be examined for evidence of discharge. If none is seen, the urethra should be gently massaged from the ventral part of the penis towards the urethral meatus. As indicated in the causative pathogens above, the major bacterial causes of urethral discharge are *N. gonorrhoeae* and *C. trachomatis*. The syndromic management treatment of a patient with urethral discharge should adequately cover these two organisms. Thus, syndromic therapy should include effective treatment for uncomplicated gonorrhea

plus effective therapy for *Chlamydia*. It is recommended that patients be advised to return, where possible, if symptoms persist 7 days after start of therapy. An example of an algorithm for urethral discharge is shown in Fig. 54.2. Table 54.1 gives current effective therapeutic options for these organisms. For purposes of compliance and acceptability single dose oral therapy, whenever possible, should be given. This combination treatment has been shown to be both highly efficacious and cost-effective. In a study in Bandung, Indonesia, the clinical effectiveness of the approach was seen in 97% of patients. The positive predictive value was high (adjusted to 97%) and the algorithm was feasible and acceptable at the primary healthcare setting.<sup>17</sup> In a multi-centre study in Brazil syndromic management of urethritis in men had a higher sensitivity for both gonorrhea and *Chlamydia* (98.8% and 91.4%, respectively) than that of a clinician's presumptive diagnosis (86.3% and 48.6%, respectively).<sup>2</sup> In this study, adding laboratory investigations improved the specificity and positive predictive value only for gonorrhea, but not for *Chlamydia*. Researchers from other parts of the world have similar conclusions for the urethral discharge syndromic management.

There is accumulating evidence suggesting high prevalence of *T. vaginalis* in men with urethral discharge. In those settings, treatment for the protozoan should be part of the syndromic

management in men, either at the first instance or when urethritis persists or recurs without re-infection.

### PERSISTENT OR RECURRENT URETHRITIS

Persistent or recurrent urethritis may be due to drug resistance, poor compliance or re-infection. In few patients, *Trichomonas vaginalis* may be the responsible pathogen, which may not have been covered in the initial treatment algorithm.

If re-infection has been reliably excluded, assessment should be made to ascertain that the first line treatment given was an effective recommended regimen. All cases of treatment failure to the first line treatment should be accurately recorded and reported to the relevant health authority. These reports will form part of the early warning system and should alert the authorities to the possibility of antimicrobial resistance in the community. A more systematic investigation should be initiated in collaboration with a national reference laboratory when cases of treatment failure occur with increased frequency or in large numbers (for example, five separate cases in a month). The public health system response then involves identifying the proportion of isolates which show resistance. When the proportion of resistant strains obtained from persons with gonococcal infection is at a level of 5% or

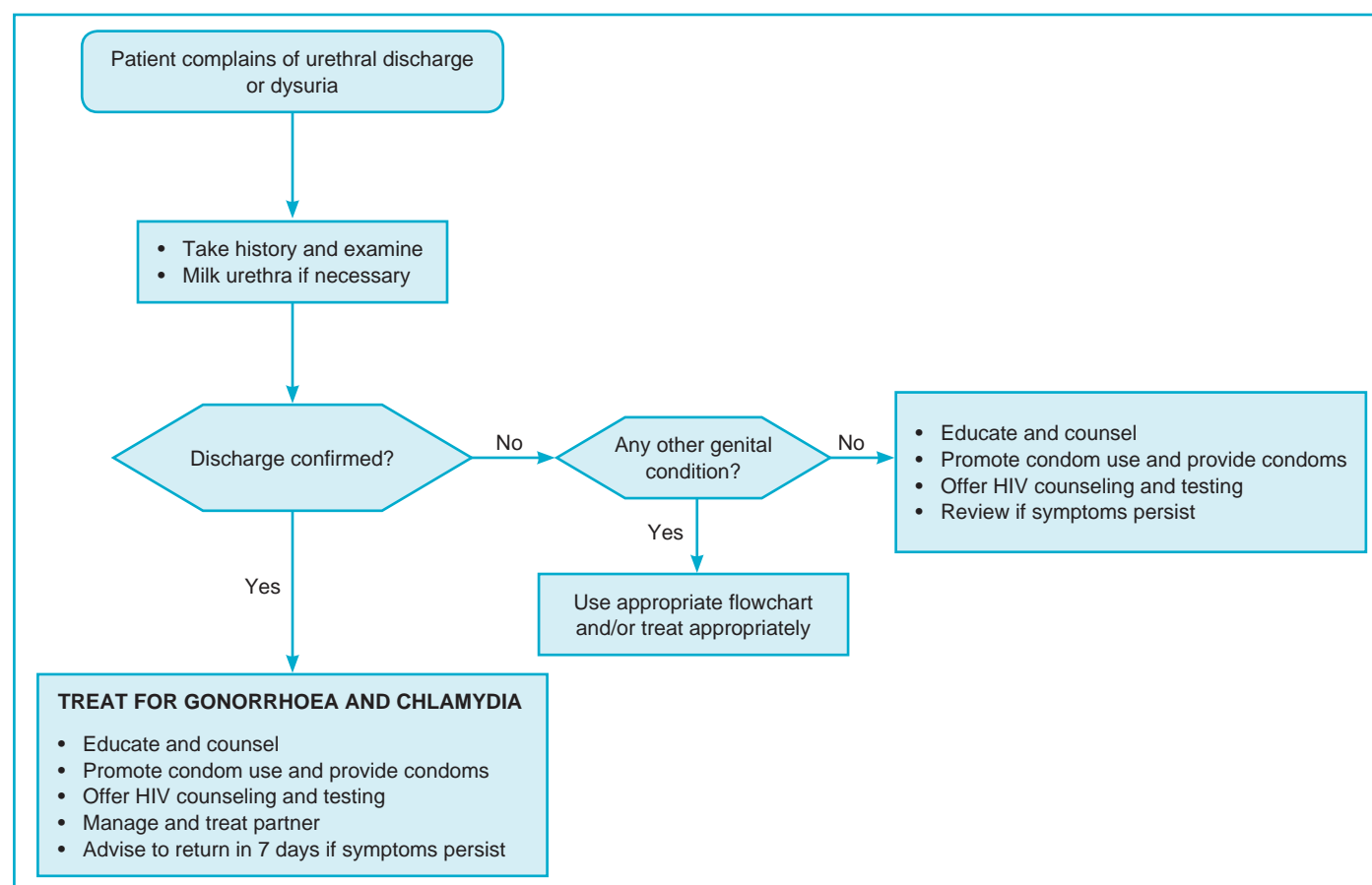


Fig. 54.2: Flowchart for the syndromic management of urethral discharge.

more, or when any resistance is detected in key populations with high rates of gonococcal infection (for instance in men who have sex with men or sex worker populations), steps need to be taken to review and modify the national treatment and management guidelines while enhancing surveillance.

Multiple drug-resistant *C. trachomatis* infection has been reported in the past. This may cause persistence of urethritis after adequate treatment in an occasional patient.<sup>18</sup> Other possible causes include infection with *Ureaplasma urealyticum* and *Mycoplasma genitalium*.<sup>19</sup>

## NOTIFICATION AND MANAGEMENT OF SEXUAL PARTNERS

The sexual partners of STI patients are likely to be infected themselves and should be offered treatment. Further transmission of STI and re-infection are prevented by referral of sexual partners for diagnosis and treatment. Female partners of male STI patients may well be asymptomatic; thus, partner notification and management offer an opportunity to identify and treat people who otherwise would not receive treatment. Partner notification should be considered whenever an STI is diagnosed, irrespective of where care is provided. Notification can be by patient referral or by provider referral. In patient referral an infected patient is encouraged to notify partner(s) of their possible infection without the direct involvement of healthcare providers, while in provider referral healthcare providers or other health-care workers notify a patient's partner(s).

Partner notification should be conducted in such a way that all information remains confidential. The process should be voluntary and non-coercive. The aim is to ensure that the sexual partner(s) of STI patients, including those without symptoms, is/are referred for evaluation. Management of sexual partners is based on knowledge of the index patient's diagnosis (syndromic or specific).

The following strategies can be adopted for the treatment of partners:

- Offer immediate epidemiological treatment (treatment based solely on the diagnosis of the index patient) without any laboratory investigation.
- Offer immediate epidemiological treatment, but obtain specimens for subsequent laboratory confirmation.

The strategy selected will depend on:

- risk of infection,
- severity of disease,
- availability of effective diagnostic tests,
- likelihood of a person returning for follow-up,
- availability of effective treatment,
- likelihood of spread if epidemiological treatment is not given,
- available infrastructure for follow-up of patients.

The WHO recommends that epidemiological treatment (with the same treatment regimen used for the index patient) should be given to all sexual partners without delay.

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# Epididymitis and Epididymo-orchitis

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# 55

## Introduction

The epididymis is elongated, tightly coiled duct of up to 4.5 meters in length situated at the posterior border of the testis. It provides for transit, maturation, and storage of spermatozoa which are formed in the testis. During passage through this length of the organ, differentiated sperm cells undergo maturation processes including motility and the potential to fertilize an egg.

## Epidemiology and Etiology

Epididymitis, an inflammation of the epididymis, is common and responsible for a significant loss of time from work for men. It is often associated with infection of the testis; in that case the term “epididymo-orchitis” is used. However, some organisms tend to cause infection only of the epididymis. It has been reported that the incidence of epididymitis may range from one to four per 1000 men per year. The average duration that men with epididymitis are absent from work is 1 week.<sup>1</sup> With increased understanding of the condition, a decrease in morbidity can be achieved. The peak incidence for epididymitis is between 20 and 29 years of age, but close monitoring is needed to capture any changes in epidemiology due to changes in sexual behavior with more and more boys becoming sexually active at a younger age.

Acute epididymitis is uncommon in infants and is usually associated with underlying genitourinary tract abnormalities. In prepubertal boys, the usual etiologic agents of epididymo-orchitis are coliforms, *Pseudomonas*, or mumps virus infections. In sexually active adolescents and men below the age of 35 years, epididymo-orchitis is mostly due to sexually transmitted pathogens such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.<sup>2,3</sup> Without the use of antibiotics, up to 30% of gonococcal urethritis may end up in acute epididymitis in this sexually active population. In older men (over 35 years of age), on the other hand, coliforms are more commonly implicated as a complication of urinary tract infection. In this older age group, the organisms commonly identified are *Escherichia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*, *Proteus*, or *Staphylococcus epidermidis*. Increasingly, coliforms are responsible for the higher risk and increased frequency of acute

epididymitis in men who have unprotected anal sex with men.<sup>4</sup> In heterosexual men, coliforms more often cause epididymo-orchitis, if there has been recent catheterization or instrumentation.

Other causative organisms of epididymitis, secondary to systemic infections, include *Mycobacterium tuberculosis*, *Brucella* spp., *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Treponema pallidum*. In post-mortem analyses, it would seem that cases of tuberculous epididymitis occur only if patients have prostatic, renal, or seminal vesicular involvement.<sup>5</sup> Furthermore, tuberculous epididymitis tends to present with bilateral inflammation in most cases compared to the mostly unilateral manifestation of coliforms and sexually transmitted pathogens. A high index of suspicion needs to be kept for tuberculous epididymitis in settings of high HIV prevalence as tuberculosis becomes more common in men in such settings. In such patients as well as in post-transplant patients on immunosuppressive therapy, it is important to keep in mind other opportunistic infections known to cause epididymitis, such as histoplasmosis, coccidioidomycosis, and cryptococcosis. Infection with *Candida albicans*, *Candida glabrata*, cytomegalovirus, and *Haemophilus influenzae* can also occur in these patients.

## Clinical Presentation

Acute epididymitis may be sudden or gradual. Clinically, the patient complains of a painful swollen testis (Fig. 55.1), which is unilateral in about 10–30% of patients with a gonococcal infection.<sup>6</sup> Men with epididymitis due to sexually transmitted pathogens, such as *C. trachomatis* or *N. gonorrhoeae*, often have a history of urethral discharge or dysuria, although some may not show any urethral signs of the infection. History of a recent sexual exposure may be obtained and would be a useful pointer to diagnosis. Epididymitis occurs in either of the testicles with equal frequency. Fever is present in approximately 75% of the patients and chills are reported mostly in elderly patients.<sup>7</sup> Pain may also be felt beyond the scrotum in the inguinal region or the abdominal flank on the affected side. Generally, younger patients below 35 years of age show less severe symptoms. The



**Fig. 55.1:** Scrotal swelling with erythema on the surface due to chlamydial epididymitis. Patient had urethritis 8 days ago, received treatment only for gonorrhea, resulting into development of epididymitis due to untreated Chlamydia.

inflammatory process begins in the epididymal tail and extends to the rest of the tube and the testicle, although inflammation of the testis itself is rare. Examination reveals an enlarged and tender epididymis on the affected side with erythema of the overlying scrotal skin in the region of the epididymis (Fig. 55.1).

Simple examination during an acute infection may not easily distinguish between the testis and the epididymis as both structures may be inflamed. The spermatic cord may be swollen and tender. Careful examination of the urethra may reveal a discharge or microscopic urethritis on a Gram stain of a urethral smear. Occasionally, there may be an accompanying inflammatory hydrocele.

## Differential Diagnosis

Testicular torsion, caused by twisting of the spermatic cord, is the most important differential diagnosis of acute epididymitis as it rapidly leads to infarction of the testis. Testicular torsion has a short history of onset and the testis usually lies higher and transverse within the scrotum. This diagnosis is more frequent in prepubertal children. Testicular torsion is a surgical emergency and surgical exploration may need to be considered in this age group.

Tuberculous epididymitis is an unusual but important form of epididymitis, and this is of relatively greater importance in

areas of high prevalence of tuberculosis.<sup>8</sup> Clinically, it is usually bilateral, non-tender, and firm to palpation. In brucellosis, usually due to *Brucella melitensis* or *Brucella abortus*, an orchitis is likely to be clinically more evident than an epididymitis.

Mumps can also cause an acute orchitis and a history of recent mumps infection should be excluded. In this infection, testicular swelling usually develops within a week of parotid swelling.

The differential diagnosis should also include other non-infectious causes of testicular swelling. These include trauma and testicular malignancy. It is important to realize that the peak ages for epididymitis are similar to those for testicular tumors. Thus, whereas a painless testicular mass almost always indicates a tumor, the presence of pain does not necessarily rule out a tumor.

There have also been reports of epididymitis in patients with Behçet disease, polyarteritis nodosa, and Henoch–Schönlein purpura. Other conditions that may complicate a clear diagnosis of epididymitis are varicoceles, herniae, and spermatoceles.

## Complications

The following are some of the encountered complications of acute epididymo-orchitis, and are usually a consequence of delayed treatment:

- Scrotal abscess
- Testicular infarction
- Infertility or decreased fertility
- Testicular atrophy
- Chronic epididymitis and orchalgia

When the inflammation is due to coliforms, severe inflammation may lead to formation of an abscess, testicular infarction, and testicular atrophy.<sup>8</sup> If not effectively treated, epididymitis can lead to decreased fertility. If patients present with bilateral epididymitis and bilateral occlusion of the vas deferens or epididymis, they may become totally infertile. Retrospective epidemiologic results also support an association between positive Chlamydia serology and male infertility. However, in most of such studies, the association does not reach the level of statistical significance due to small sample size.<sup>9</sup> Chronic epididymitis presents with unilateral or bilateral scrotal pain, sometimes associated with chronic testicular pain (chronic orchalgia), either intermittent or persistent for three or more months in duration. The etiology can be associated with inflammatory, infectious, or obstructive factors but, in many cases, no identifiable etiology can be identified.<sup>10</sup>

## Laboratory Diagnosis

Where laboratory investigation is possible, examination of the urine and urethral smear is a very helpful procedure in differentiating epididymitis from testicular torsion. Urine microscopy should be performed to detect pus cells. Torsion does not give rise to pyuria. A midstream urine sample, without centrifugation, can be useful to make a presumptive diagnosis of epididymitis, if bacteriuria is confirmed as in the case of coliforms and *Pseudomonas* infections. A midstream urine culture should

be performed in all cases of suspected epididymitis. A Gram stain of a urethral smear may aid in the diagnosis of *N. gonorrhoeae*. Detection of *C. trachomatis* should also be attempted, where possible, as this pathogen can be the sole cause of epididymitis without *N. gonorrhoeae* or other pathogens.<sup>2</sup> Culture of an epididymal aspirate has been tried to establish a diagnosis of epididymitis in special circumstances. This is not recommended in an out-patient consultation. Some of the special cases that warrant this procedure are recurrent epididymitis in which the etiologic agent cannot be established, failure to respond to effective antimicrobial treatment and epididymitis found on surgical exploration for suspected testicular torsion.

In many settings, however, a laboratory diagnosis cannot be performed for reasons of cost, lack of diagnostic equipment or lack of trained laboratory technicians. In such cases, a syndromic approach to the management of testicular pain and swelling should be followed.

## Syndromic Management of Acute Scrotal Swelling

If history suggests it and a urethral discharge is detected then the epididymo-orchitis is most likely secondary to either or both of the sexually transmitted pathogens, *N. gonorrhoeae* and *C. trachomatis*. It should be remembered that the absence of a urethral discharge does not exclude the presence of STI—history is, therefore, of paramount importance in making the decision. For example, in a report of young military recruits with epididymitis, 16% had gonococcal infection, but only 50% of them with the infection had urethral discharge.<sup>11</sup> Figure 55.2 shows a flow chart that can be used to assist in the syndromic management of a scrotal swelling or scrotal pain. If no laboratory diagnosis is possible, it is recommended that the patient be treated at the same time for the two pathogens (Fig. 55.2). Generally, the management of the

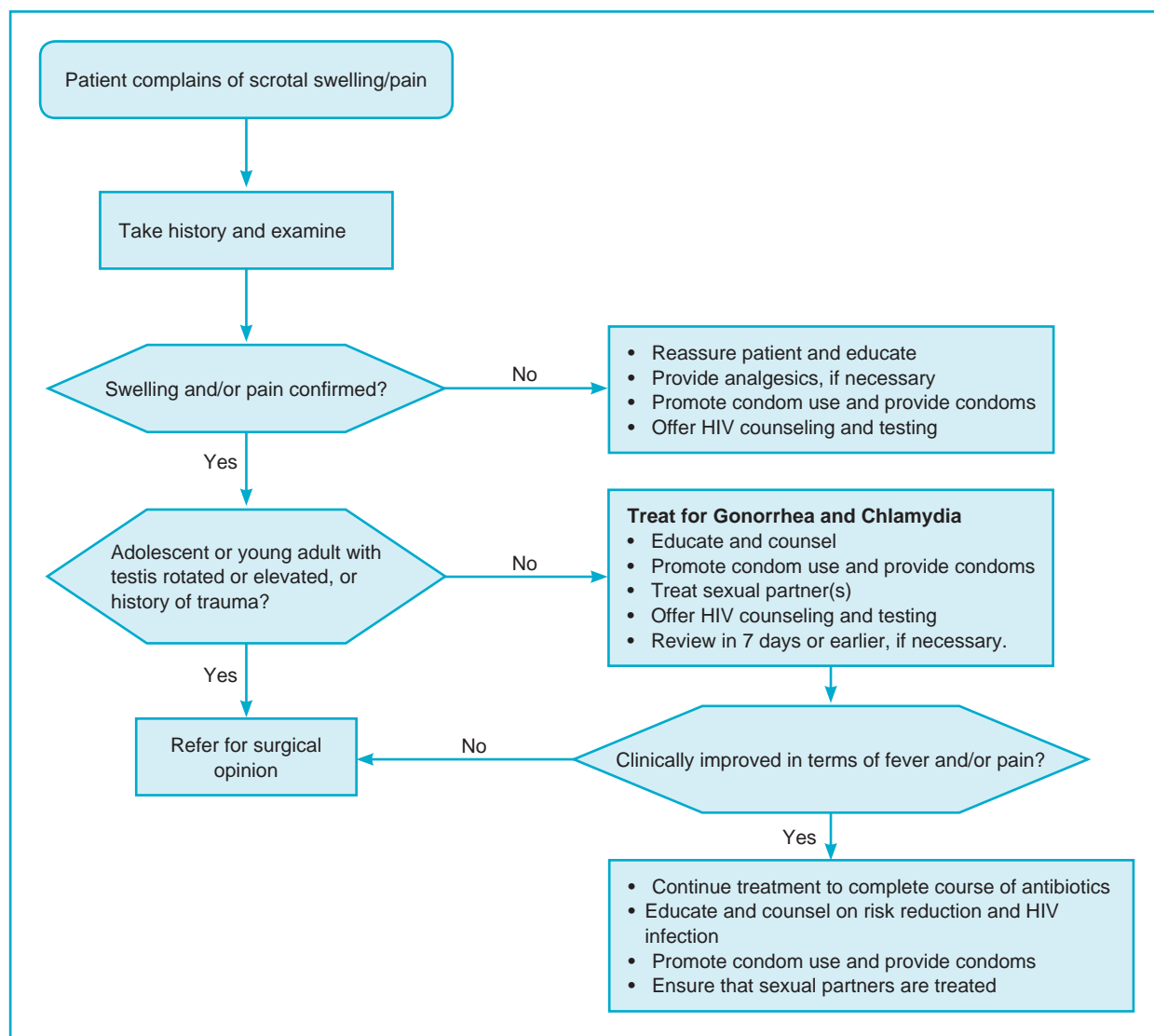


Fig. 55.2: Scrotal swelling management flowchart.



patient includes bed rest, scrotal support and elevation, pain relief, and appropriate antibiotics. Elevation can be achieved by placing a towel, or some other such material, between the patient's legs while in the supine position. While lying down, scrotal support alone is not sufficient as the scrotum would be dependent and drainage will be delayed. Bed rest should be continued until tenderness has resolved. Pain relief can be provided by the use of non-steroidal anti-inflammatory drugs. Various other combinations have been tried and shown to hasten the disappearance of pain ahead of inflammatory resolution. Injection of the spermatic cord with xylocaine hydrochloride has been shown to relieve pain immediately and more effectively than the use of antibiotics alone.<sup>12</sup>

Syndromic treatment should be as follows:

- Effective therapy for uncomplicated gonorrhea plus effective therapy for Chlamydia. A possible syndromic regimen, after taking into account locally determined antimicrobial susceptibility patterns, may include:
  - ceftriaxone, 250 mg, IM, single dose for gonococcal infections PLUS
  - doxycycline, 100 mg, orally, twice daily for 10 days or azithromycin 1 g orally as a single dose, for chlamydial infections.
- Patients in whom gonorrhea and/or Chlamydia are suspected to be the cause of the epididymitis, management of sexual partners must not be overlooked. Sexual partners should be treated for the same infections as the index patient.
- For acute epididymitis most likely caused by enteric organisms, appropriate antibiotics should be given. For example, ofloxacin, 400 mg orally, twice daily for 10 days or levofloxacin 500 mg once daily for 10 days. As *E. coli* and other coliforms are demonstrating increasing resistance to trimethoprim-sulfamethoxazole, this combination antibiotic should not be used without laboratory guidance in terms of susceptibility of the organism.
- For severe infections, consideration should be given to intravenous broad-spectrum antibiotics directed against coliforms and *P. aeruginosa*.

Potentially epididymitis has serious consequences in young people. Therefore, more effort should be made to prevent it from occurring. Urethritis should be treated effectively and promptly at the first port of call for any patient. When epididymitis occurs treatment should be prompt. No justification can be made to withhold the use of antibiotics in suspected infectious epididymitis.

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# Abnormal Vaginal Discharge: Syndromic Management

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# 56

## Definition

The term vaginal discharge has been used synonymously with leukorrhea. It has been defined as whitish discharge, which is not associated with menstruation. When used by the patient, it is considered a symptom, the clinician uses it to describe a sign, and sometimes as diagnosis. As the pathophysiology is becoming more clearly understood, it is apparent that the term “*leukorrhea*” is ambiguous. The symptoms and signs of vaginal discharge are found in diverse physiological to pathological conditions, both local and systemic disturbances. Abnormal vaginal discharge (AVD) is defined as any one of the three presentations: (i) excessive vaginal discharge not associated with menstruation, pre-, mid-, and post-period; (ii) offensive or malodorous discharge; and (iii) yellowish or mucopus discharge.<sup>1</sup>

Vaginal discharge is the most common presenting complaint in women attending gynecologists, general practitioners, and various health clinics for women.

Discordance between degree of AVD as described by the patient and examination findings may occasionally be encountered. Some patients can tolerate persistent discharge without complaint, and eventually deny its presence, although speculum examination shows heavy discharge. On the other hand, many patients complain of offensive/profuse discharge, however, speculum examination reveals no odor/discharge. Patients that need to be investigated include those presenting with symptoms of AVD, with or without concurrent urogenital symptoms.

## Prevalence

It has been estimated that up to one-third of female patients may complain of AVD, however, there are no epidemiological data to support this. AVD can occur in females of all ages, from the neonatal to the postmenopausal period, and it is quite common during pregnancy. Many clinics have reported that more than 70% of pregnant women manifest AVD, due to lower genital tract infection (LGTI).<sup>1</sup> In a study of 240 females of reproductive age with AVD, the prevalence of various causative conditions had been found to be 37.9% for bacterial vaginosis (BV), 33.7%

for mucopurulent cervicitis (MPC), 29.1% for non-infective leukorrhea (NIL), 22.0% for vaginal candidiasis (VC), and 4.1% for vaginal trichomoniasis (VT). Among these 240 women, 15.8% had infection with two organisms, and 0.4% with more than two organisms. Detection of *Chlamydia trachomatis* from endocervical secretion of women who had MPC is obtained up to 12.3%. One-sixth of infective causes are mixed infection.<sup>2</sup>

## Normal Discharge

The normal discharge is floccular in consistency (similar to coarse granules of cassava starch gluten), whitish, and non-malodorous. The volume may vary considerably between individuals, from minimal staining of undergarment to profuse discharge. The normal pH is acidic, ranging from 3.5 to 4.5 due to activity of Döderlein lactobacilli, which convert glycogen into lactic acid. Acid pH may exist even when lactobacilli are decreased in number or absent. This is thought to be due to secondary fermentation of endocervical mucus by vaginal flora.<sup>3</sup> Therefore, a decreased number of lactobacilli do not always imply infectious conditions.

The vaginal pH rises to 7.0 within just seconds after ejaculation.<sup>4</sup> Cervical pH is alkaline, with a peak pH during the periovulatory period.<sup>5,6</sup> The cellular contents of the discharge are composed of sloughed cells of cervical columnar and vaginal squamous epithelium. The bulk of discharge consists of serous vaginal transudate and lubricating cervical mucus.<sup>1,7-9</sup>

## VULVOVAGINAL SOURCE

The vaginal canal, being of ectodermal origin, consists of stratified squamous epithelium. There are no sweat, sebaceous, and other types of secretory glands in vaginal epithelium. The *portio vaginalis* of the cervix, derived from Müllerian duct system, projects into the upper end of vagina. At the caudal end is the vulva, lined by squamous epithelium; containing secretory, sweat and sebaceous glands, and hair follicles. The paraurethral (Skene glands) and greater vestibular (Bartholin) glands are located at each side of the vestibule. Skene glands are vestigial tubules, 1–2 cm in length, lined with columnar epithelial. Bartholin glands

are tubuloalveolar mucous glands, with acini lined by columnar epithelium. The mucus secretions of these glands bathe the surface of the vestibule and the introitus, but probably contribute little increment to the vaginal secretions.<sup>1</sup>

Vaginal fluid is largely derived from serum transudate in vaginal beds that seeps from capillaries through intercellular channels. Smaller amount of fluid is derived from Bartholin glands, endometrium, and fallopian tubes. White blood cells are present only in small numbers in women without LGTI.<sup>10</sup> Beside cellular debris, the vaginal transudate is principally composed of water and electrolytes, facultative microorganisms, and organic compounds such as fatty acids, proteins, and carbohydrates.<sup>11</sup>

BV is characterized by an absence of lactobacilli and, thus, an elevated pH. A low vaginal pH may inhibit CD4 lymphocyte activation and therefore decrease HIV target cells in the vagina;<sup>12</sup> conversely, an elevated pH may make the vagina more conducive to HIV survival and adherence.<sup>13</sup>

Hormonal change, “sex steroid hormone starvation” results in a decreased genital blood supply, loss of vulvar adipose tissue, an increase in pH to above 5.0 of the vaginal secretions, thus predisposing the vagina to infection.<sup>8,14</sup> In addition, desquamation of the mature epithelium and traumatization of the mucosa may result in a break of its continuity, allowing bacterial penetration and possible infection.

## CERVICAL SOURCE AND BEYOND

The cervix is a principal source of vaginal secretion. The stratified squamous epithelial lining of the *portio vaginalis* is continuous with vaginal fornices. At the external os, this epithelial surface changes abruptly to a high columnar epithelium, which lines the cervical canal up to the internal os, and lines the cervical glands as well. The cervical glands are of simple and tubuloalveolar type that secrete thick and viscid mucus.

The uterus contributes little to the secretion of vaginal canal, despite the presence of endometrial surface and numerous glands, lined with highly secretory columnar epithelium. The secretion of these cells undergoes cyclic activity in the elaboration of glycogen, and other nutritive materials in preparation for pregnancy each month. Under normal circumstances, the fallopian tubes contribute nothing to the vaginal secretion. Only in rare instance of a hydrosalpinx, resulting from a salpingitis, it is conceivable that tubal secretions may be expelled into the vagina, in the form of a watery discharge.<sup>1</sup>

## Vaginal Microorganisms

In a healthy woman, the vaginal flora consists of a variety of organisms. Besides *Lactobacillus* and *H2O2*-positive *Lactobacillus*, it may also include anaerobic gram-negative rod, *Bacteroides ureolyticus*, beta-hemolytic and non-hemolytic streptococci, *Candida albicans*, diphtheroids, enterococci, *Escherichia coli*, *Fusobacterium nucleatum*, *Mobiluncus* spp., *Mycoplasma hominis*, *Micrococcus pyogenes*, *Peptostreptococcus* spp., *Prevotella bivia disiens*, *Staphylococcus epidermidis*, and *Ureaplasma urealyticum*.

*Lactobacillus* species have been recovered from 96% of the normal women, whereas, coliforms are more common in the vagina before puberty than after puberty. The lower genital tract resembles the nasopharynx in many aspects, such as epithelial surface and mucous secreting glands. Both are affected in the same way by inflammation and physiological changes. There have similar microbiological flora except *E. coli* and other intestinal organisms, which are present only in the genital tract.<sup>1,15–18</sup>

The vaginal ecosystem is a complex environmental condition, consisting of interrelationships among the endogenous microflora, metabolic products of the microflora, host estrogen, and the pH. Vaginal inflammation and infection occur when the vaginal ecosystem is altered. When the balances of microorganisms' changes, potentially pathogenic endogenous microorganisms that are part of the normal flora (e.g., *C. albicans* in cases of VC, and *Gardnerella vaginalis* synergistic with anaerobic bacteria in cases of BV) proliferate and lead to overt infection. Little is known about factors that contribute to the overgrowth of normal flora. Exogenous sexually transmitted microorganisms such as *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis* are the pathogenic agents.

## Etiological Factors

Apart from being physiological and non-infective conditions, four major causes of cervicitis and vaginitis include MPC, BV, VC, and VT. Infections of the cervix represent a reservoir of pathological microorganism, and may lead to two possible types of complications: (i) ascending intraluminal spread from the cervix often produces endometritis (silent pelvic inflammatory disease [PID]) and eventually acute salpingitis (overt PID); and (ii) ascending infection during pregnancy results in chorioamnionitis, premature rupture of membrane, premature delivery, amniotic fluid infection, and puerperal infection.<sup>19</sup> The systematic approach of AVD will make the diagnosis easy and reduce the rate of complications. Table 56.1 shows the possible etiologic causes of AVD.<sup>20</sup>

## Age-Dependent Physiological Condition

During the first month of life still under the influence of maternal estrogen, the neonatal vagina is lined by stratified squamous epithelium. From the 1 month of age until puberty, the vagina is lined by cuboidal cells, and the pH of the vagina fluid is about 7.0, neutral, or alkaline pH. After puberty, the vagina is lined by stratified squamous epithelium, which becomes much thinner after menopause.<sup>19</sup>

## NEONATE AND INFANT

Neonatal physiological discharge results from the mature stratified squamous epithelium cells under the influence of maternal estrogen. Maternal estrogen is metabolized by 3–4 weeks of age. In early neonate period, the vaginal epithelium is susceptible to with *T. vaginalis* and *C. albicans* due to perinatal transmission, but resistant to *N. gonorrhoeae* and *C. trachomatis*. In the late neonate period, after 1 month of age, vaginal epithelium returns



**Table 56.1:** Causes of Abnormal Vaginal Discharge

Physiological
Age-dependence
Neonate and infant
Prepuberty
Childbearing
Postmenopausal
Excessive secretion
Pregnancy
Sexual arousal
Pathological
<b>a) Non-infective</b>
Chemical irritations
Antiseptics
Bath additives
Deodorants
Detergent spermicides
Douches
Perfumed soaps
Foreign bodies
Intrauterine contraceptive device (IUCD)
Retained materials
Retained tampons
Retained sheaths
Gynecological conditions
Endocervical polyp
Fistulae
Radiation effects
Post-operative
Tumors
Medication, nutrition and sexual practice
<b>b) Infective</b>
Cervicitis
Herpes genitalis
Mucopurulent cervicitis (MPC)
Gonococcal MPC (gonorrhea)
Nongonococcal MPC
Chlamydia positive form
Chlamydia negative form
Vaginitis
Bacterial vaginosis (BV)
Vaginal candidiasis (VC)
Vaginal trichomoniasis (VT)

Modified from Blackwell.<sup>20</sup>

to a prepubescent stage, and silent shedding of *C. trachomatis*, due to perinatal infection, sometimes occurs.

In older infants, the vaginal cuboidal epithelium is susceptible to *N. gonorrhoeae* and *C. trachomatis* but resistant to *Candida*. Nevertheless, the vaginal infection is rare among infants. *N. gonorrhoeae* is an exception, and thought to represent postnatal acquisition, and is often symptomatic. *C. trachomatis* does not generally reveal the overt signs of infection.<sup>19,21,22</sup>

Typically, neonatal and infantile LGTI are asymptomatic, and the only complaint that the mother notices, is a yellowish stain on the child's diapers or panties.

## PREPUBERTY

Pubertal physiological discharge is a frequently indicative hallmark of impending onset of menarche.<sup>23</sup> Prior to menarche,

the unopposed secretion of estrogen from the ovaries stimulates vaginal and cervical secretion. The discharge during this period is thin and mucoid, which infrequently soils the undergarment. This discharge may be interpreted by an adolescent or her mother, as an evidence of infection.<sup>24</sup> It ultimately subsides with the onset of cyclic progesterone activity.

## CHILDBEARING AGE

The amount of discharge is usually sufficient to keep the vaginal wall moist, but usually not stain the undergarment. The discharge may be sufficient to soil few areas of the undergarment in pre- and post-menstrual period. The discharge often transiently increases in the mid-cycle due to stimulation of the endocervical glands by estrogen. Concurrently, Mittelschmerz or mid-cycle unilateral pelvic discomfort associated with ovulation is not uncommon, usually mild, and rarely lasts more than 24 hours.<sup>25</sup> These cyclic variations do not occur when combined (estrogen and progesterone) or progesterone-only contraceptive pills are used, and the ovulation does not occur.

Occasionally, excess fluid may result from exogenous sources, such as semen of recent ejaculation, vaginal douches, and intrauterine contraceptive device (IUCD).

## POSTMENOPAUSAL PERIOD

Following menopause, marked atrophic changes occur in the vaginal epithelium according to diminished estrogen secretion. Occasionally, because of these atrophic changes, there is a thin, serous discharge, which is stained with blood and associated with itching and burning. Small areas of granulation and ulceration along with slight vaginal bleeding may develop.<sup>1</sup> In postmenopausal women, the most common cause of AVD is atrophic vulvovaginitis.

## Excessive Secretion

### PREGNANCY

Physiological discharge, floccular in characteristics, of pregnant women may exceed than 1 ml of amount on speculum examination, due to increased vascularity, congestion of pelvic organs, and cervical hyperplasia. Moreover, the cervix is likely to bleed during pregnancy, owing to direct trauma from penile thrusting.<sup>26</sup>

### SEXUAL AROUSAL

In nonpregnant women, sexual arousal results in an increased discharge, due to secretion from Bartholin glands. The amount of discharge is increasing during pregnancy, and augmented during sexual arousal.<sup>7</sup>

### NON-INFECTIVE CONDITIONS

#### Chemical Irritants

Using of antiseptics, bath additives, deodorants, detergent spermicides, douches, and perfumed soaps can cause chemical

induced vulvovaginitis. Allergic reactions rarely cause the discharge, but often present local reaction. The patient should be advised to avoid the use of such substances. Saline bath may help to reduce vulvar irritation in the acute phase.

Long-term use of tampons has to be avoided, preventing vaginal ulceration. Although the practice of vaginal cleansing should generally be discouraged, some women insist on douching, in which case, mild vinegar solution or water can be used. Multiple douches may increase the amount of discharge, due to drying effect. Douching with commercial preparation leads to cause abnormal shifts in vaginal flora.<sup>27</sup> Intravaginal application is discouraged because of its link with PID.<sup>28</sup>

## Foreign Bodies

Foreign body in the vagina is relatively an uncommon cause of increased vaginal discharge. Cotton wool from tampons often becomes entwined with the thread of IUCD and then acts as a focus for secondary bacterial infection. Similarly, retained tampons and broken sheath may result in persistent bacterial infection, producing a copious, foul smelling discharge. It is necessary to remove the foreign body, and then the vaginal flora will rapidly return to normal.<sup>20</sup>

## GYNECOLOGICAL CONDITIONS

Endocervical polyp may produce a mucoid secretion and blood-tinged discharge. Profuse watery discharge without mucoid element is suggestive of urine, and its presence in the vagina is likely to be urogenital fistula. Urogenital fistula can be caused by radiation.

Following hysterectomy, vaginal vault granulation tissue may result in the excessive discharge of clear character, and eventually slight bloody secretion. All the tumors, whether benign or malignancy in their early stages, can produce the discharge. In benign tumors, the genital secretion can become quite heavy when the size of the tumor increases. Malignant tumors quickly change to produce a blood-stained discharge or flank bleeding quite early in the process. Secondary bacterial infection may add a purulent element to the discharge.

## MEDICATION, NUTRITION, AND SEXUAL PRACTICE

Alternative medicinal drugs, over the counter (OCT) medical products, and nutritional compounds may be associated with either infective or non-infective discharge.<sup>29</sup> These products include antibiotics, antifungals, antiseptics, and hormonal preparations. General health and sexual practices can affect the balance of microorganisms. Vaginal douches, sexual activities, and change in partners sometimes alter the delicate equilibrium of vaginal flora.<sup>30,31</sup>

Use of doxycycline, azithromycin, clotrimazole, and fluconazole has little effect on vaginal colonization by *Lactobacillus*. Uses of oral and vaginal metronidazole lead to an increase in *Lactobacillus*, which has persisted 1 month after therapy. Intravaginal clindamycin use has caused a decrease 1-week

post-therapy, but at 1 month, level of lactobacilli is similar to those in the metronidazole treatment group. Women treated with oral ampicillin have a modest increase in *Lactobacillus* level. Antimicrobial agents, treating vaginitis and cervicitis, do not cause a decrement in colonization of *Lactobacillus*, detecting 1 week to 1 month after therapy.<sup>32</sup>

## INFECTIVE CONDITIONS

Herpes genitalis in its acute stage, when vesicles and superficial ulcers are present, may give rise to vaginal discharge. BV caused by the synergy of *G. vaginalis* and anaerobic bacteria, a set of BV organisms, is a commonest cause of AVD.<sup>2</sup> Other causative pathological organisms include *C. albicans*, *T. vaginalis*, *C. trachomatis*, and *N. gonorrhoeae*. Genital lesions (e.g., warts, syphilitic chancre, chancroid, etc.) may produce discharge. However, there is some doubt whether *M. hominis*, *M. genitalium*, *U. urealyticum* do cause vaginitis and cervicitis.

## Approach to a Patient with AVD

### GENERAL CONSIDERATIONS

AVD develops when the vaginal flora has been altered by the changes in the vaginal environment, or by the introduction of a pathogen that allows the pathogen to proliferate. Despite a limited number of causes, the clinicians often have difficulty in establishing an accurate diagnosis of AVD. The identification of the etiological causes is often over-diagnosed among women, who actually have normal flora. Mixed infection occur frequently, the assessment may be under-diagnosed as one cause.<sup>9</sup> The approach of AVD may be complicated by the wide variety of vaginal preparations available, many of which are self-prescribed and self-administered. With attending their clinicians again and again, persistent symptoms often lead to patients' dissatisfaction, and then switch to seek for a second opinion.

Persistent symptom brings to high cost of repetitive visits, in managed healthcare systems. The frequent failures to relieve symptoms, lead to a high rate of doctor-patient frustration, and deteriorate the relationship. Beside therapeutic failure and drug resistance, the existence of AVD may be caused by sexual reacquisition, nonsexual recurrence, and depressed cellular immunity. Therefore, accurate diagnosis is an important factor in determining therapeutic success of re-treatment, if AVD is persistently occurred.

The approach of women, presenting with vaginal discharge, is not straightforward as that of urethral discharge in men. Infective and/or non-infective conditions often cause symptoms and signs of AVD. Initially, infective causes need to be treated effectively as quick as possible. It is not a simple solution for the management of AVD in the primary healthcare setting; of course, it is not the approach which aims to treat all four infections as a routine method. This would mean unacceptable overtreatment.<sup>33</sup> Local health clinic level, where speculum examination is possible without laboratory facilities, a complete of speculum examination

is recommended. The settings where laboratory supports are available, appropriate investigations will promote the accurate diagnosis. The diagnostic skills, variety of the laboratory tests, depend on a regular performance and accumulation of learning by doing.

The following list provides the whole concerned approach of AVD.<sup>34</sup>

- Symptoms of AVD are only suggestive data. Symptoms alone are not reliable for the diagnosis, while the obvious signs and characteristics of the discharge are partially accurate to make the diagnosis.
- The diagnosis is confirmative evidence, it depends on demonstration of etiological pathogen in single organism conditions such as VC, VT, herpes cervicitis, and gonococcal MPC, or else, bases on clinical diagnostic criteria in multiple organism conditions, for example, BV, chlamydial positive and chlamydial negative form MPC. Not frequently, MPC coexists with vaginitis, particularly BV or VC, whilst BV is always coexisted with VT.<sup>2</sup> The range of diagnosis varies from epidemiological, presumptive, clinical, and definite diagnosis.
- The therapy should include a regimen of at least 95% efficiency for gonorrhea, and at least 85% for other infective conditions, except better regimens are not available.
- Drug acceptability may influence the result of the treatment, and this is due to potential pitfalls of drug administration. Oral drugs are more compliant than injectables. Whereas, single dose and shorter duration are more favorable than longer therapy. In addition, adverse drug effects, and cost of therapy, should be considered as well.
- Prompt treatment for sexual partner(s) of the women with gonococcal MPC, nongonococcal MPC, and VT, prevents the rate of “table tennis phenomenon,” and reduces the transmission of disease, therefore, decreases the frequency of occurrence and adverse sequelae of infection.
- All the patients are recommended to evaluate for the result of therapy. The test of cure is categorized into (i) complete response, the clinical manifestations are relieved and the diagnostic indicators/criteria are negative; and (ii) partial response, the patients are asymptomatic carrier; and (iii) the no response, the clinical manifestations are persisted and the diagnostic indicators/criteria are positive. When test of cure reveals partially response or resistance, re-treatment and retest of cure are required. The coexisting between infective AVD and non-infective AVD can be occurred simultaneously. When the infective causes are eradicated, confirmed by the diagnostic pointers are negative, non-infective condition should be considered if AVD is still persisted.

## HISTORY TAKING

The history taking is initially obtained with three close-ended questions: (i) do you have an excessive vaginal secretion, not associated with menstruation, e.g., occurring every day or nearly every day?; (ii) whether vaginal discharge is associated

with unpleasant odor?; and (iii) whether the discharge is yellowish in color? If the answers are positive in screening questions, concomitant symptoms are then be probed, such as fever, pelvic pain, pelvic discomfort, external and internal dysuria, burning pain of the vulva, perineal/vulvar itching, superficial dyspareunia, redness of the vulva, any lumps or swellings, and ulceration of the perineum. The specific details about the recurrent or resistant infection, previous diagnoses, former treatments and their effects, menstrual history, pregnancy, and sexual practice are inquired.<sup>35</sup>

A rapid onset of AVD suggests an acute infective condition, and secondary to trauma or chemical agents. A gradual onset relates with neoplasms, silent PID, and atrophic vulvovaginitis. Discharge occurring within 24 hours of coitus suggests local trauma, reaction to smegma, and sensitive reaction to barrier method of contraception.

Change of sexual partner and recent multiple sexual contacts are suggestive sexually transmitted infections (STI). Multiple sexual partners in the sexual contact of the patient may also indicate a sexually acquired infection.

Patient's each statement should be given a careful thought as it may point towards diagnosis. For example, premenstrual exacerbation of vaginal discharge points towards VC and TV, repeated antibiotic utilization promotes VC.

## ASSOCIATED SYMPTOMS

External dysuria is limited as pain and burning when urine touches the vulva. Internal dysuria is defined as pain inside the urethra, usually a sign of acute cystitis.<sup>36</sup> Approximately 10% of women with dysuria have vulvovaginitis. External genitalia lesions associated dysuria, usually are characterized as a burning sensation. Dysuria associated AVD is suggestive of LGTI, as well as, a few numbers of urethritis, may atypically present with AVD.

Superficial dyspareunia associates not only coital discomfort, but also the lesions of external genitalia.

Pelvic pain and pelvic discomfort are quite similar, and misleading make clinical correlation difficult. Pelvic pain plays an important role in gynecological conditions, however, the exact relationship between characteristics of pain and gynecological pathology should be analyzed carefully.

Acute pelvic pain that implies to PID is mainly continuous, bilateral, and most severe in the lower quadrants. It frequently increases with movement, Valsalva maneuver, and sexual intercourse. Acute pelvic pain presents for a short duration, less than three week. Acute pelvic pain in PID is less than 15 days in 83% of patients with visually confirmed the disorder. Acute pain mostly occurs within one week in two thirds of patients with gonococcal PID. While the onset of pain in nongonococcal PID occurs steadily throughout the menstrual cycle.<sup>37</sup> A history of prolonged and inconstant pain is not likely to be PID.

Chronic pelvic pain is usually prolonged duration, 6 months or more. The gray zone, between the duration of three weeks to less than six months, may consider as subchronic symptom.



Pelvic discomfort, much more frequent symptom, is generally intermittent, diffuse, and mild intensity in the lower abdomen. Acute and chronic pelvic discomfort can be resulted from LGTI, postoperative adhesions, sequelae of pelvic infection, intrauterine contraceptive device, uterine fibroid, adenomyosis, pelvic relaxation, chronic endometriosis, endometrial polyps. In addition, musculoskeletal, urogynecological, gastrointestinal, and psychological conditions can cause pelvic discomfort as well.<sup>38</sup>

## PHYSICAL AND GENITAL EXAMINATION

General and abdominal should precede the speculum and pelvic examination. Lower abdominal tenderness on abdominal examination is likely related with upper genital tract infections, but not LGTI.

External genital examination is a step to identify genital changes. Close inspection of the external genitalia is useful in looking for atrophic condition, blisters, edema, enlarged lymph nodes, erythema, excoriation, fissure, inflammation, lesions, pallor, papillary structures, thinning, masses, and ulceration.

Speculum examination is not only helpful in inspection of lower genital canal, but also profitable in picking up the endocervical and vaginal secretion. Antiseptic agents should not be applied on the external genitalia before speculoscopy and pelvic examination to avoid vaginal contamination. It leads to false-negative outcome in wet mount preparation for *T. vaginalis* and bacteriological isolation, and false-positive outcome on the pH paper test for alkaline pH.

Warm water provides sufficiency lubrication for speculum insertion. The smallest warm speculum necessary to produce adequate visualization should be the choice. Following insertion, all aspects of vagina and cervix should be inspected under good light source. Particular attention should be paid to vaginal fornices for the lesions such as warts.<sup>39</sup> A very black, tarry type of discharge indicates that there are long-term retention of blood within the genital canal.

The accessibility of uterine cervix provides an opportunity to collect the specimens. The endocervical mucus should be separately collected and examined apart from the vaginal secretion. If cervix is dirty, it should be wiped with a large swab or gauze sponge. The endocervical specimen is then picked up by insertion of a small cotton swab into the endocervical canal.

The term “ectropion” or “ectopy” describes the exposed endocervical columnar epithelium of patulous parous cervix, when the blades of vaginal speculum are separated. Cervical changes over reproductive period and during the menstrual cycle give rise the confusion between actual cervicitis and normal cervix.<sup>40–42</sup> Ectopy or ectropion requires no therapy, in case of absence of visible and microscopic mucopus, and normal colposcopic findings.<sup>19</sup>

Pelvic examination, abdomino-vaginal bimanual palpation, is greatly meaningful in identify local gross anatomical conditions. On pelvic examination, the cervical, uterine, and adnexal tenderness should be based on facial expression of the patients for clues of the patients’ degree of pelvic conditions. The misleading of false-positive tenderness is forceful bimanual examination, and vaginal

discomfort on pelvic examination. So, the cervical tenderness on motion is gently evaluated the mobility, by attempting to displace it anteriorly and posteriorly and from side to side, then the uterus is bimanually palpated. It may be helpful to assess the cervical, uterine, and adnexal tenderness by performing the examination with moving/palpating only one finger of one hand insert into the cervix, posterior, and then both lateral fornices. The other hand with palmar surface mildly presses for evaluation of uterine and adnexal tenderness. If the patient shows a facial expression of pain, with or without specific complaint in one region, it is preferable to start the examination in the different location.

## INVESTIGATION OF ENDOCERVICAL AND VAGINAL DISCHARGE

The endocervical and vaginal specimens are recommended to have macroscopic and/or microscopic examination. Moreover, the laboratory tests vary from the level of peripheral (simple office), intermediate, and advanced laboratory should be performed as appropriate.

### Appearance of Endocervical Discharge

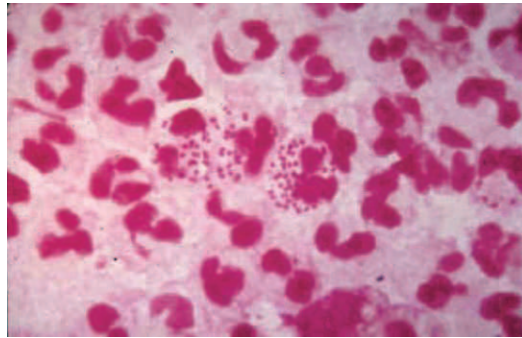
After the ectocervix is wiped clean with a large cotton swab, endocervical mucus is collected on a white-tipped swab, with care taken to avoid contamination by the vaginal secretions. The characteristics of endocervical secretion can be classified into mucoid, cloudy, and mucopurulent. Yellowish color on the white cotton-tipped swab, in contrast to any dark material, is considered as “visible mucopus.”

### Endocervical Smear Stain

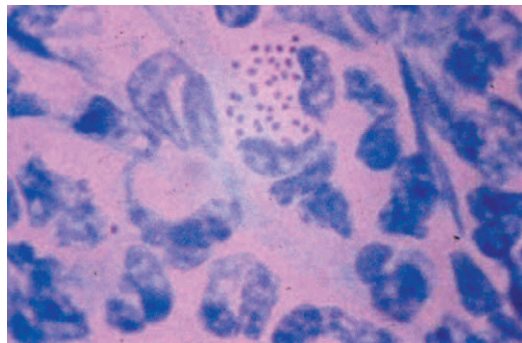
The same swab is rolled onto an area of 1–2 square cm, on a microscopic slide. Usually, the smeared secretion is distributed in separated heterogeneous islands, not homogeneous fashion.

The smear is heated dry and stained with methylene blue, safranin or conventional Gram stain. Immersion oil is added, and the microscopic slide is scanned to evaluate the presence and amount of cervical mucus, to look for contaminated squamous cells and microorganisms, and to identify areas of mucus that contain inflammatory cell. Most often, polymorphonuclear (PMN) leukocytes are not uniformly distributed in the cervical mucus, thus, in cases which they are distributed in a patchy fashion. Representative areas containing the dense concentration of such leukocytes are selected. The “microscopic mucopus” is defined as the presence of 10 or more PMN leukocytes per X 1,000 (oil field) on a smear-stained specimen of endocervical mucus at least five separated area.<sup>43</sup> The demonstration of intracellular diplococci, kidney-shaped organism (at least three pairs or more) is strongly suggestive of *N. gonorrhoeae* infection (Fig. 56.1 a and b).

The large surface area of endocervical columnar epithelium may give rise to a large amount of endocervical secretion, typically excessive in mid-cycle. Smear of the mucus with a few leukocytes, suggest physiological endocervical discharge.



\*c+



\*d+



\*c+



\*d+



\*e+



\*f+

**Fig. 56.1:** Intracellular diplococci, kidney shapes, and at least three pairs or more is suggestive of *N. gonorrhoeae*. (a) gram stain (oil field). (b) methylene blue stain (oil field).

### Methylene Blue Staining

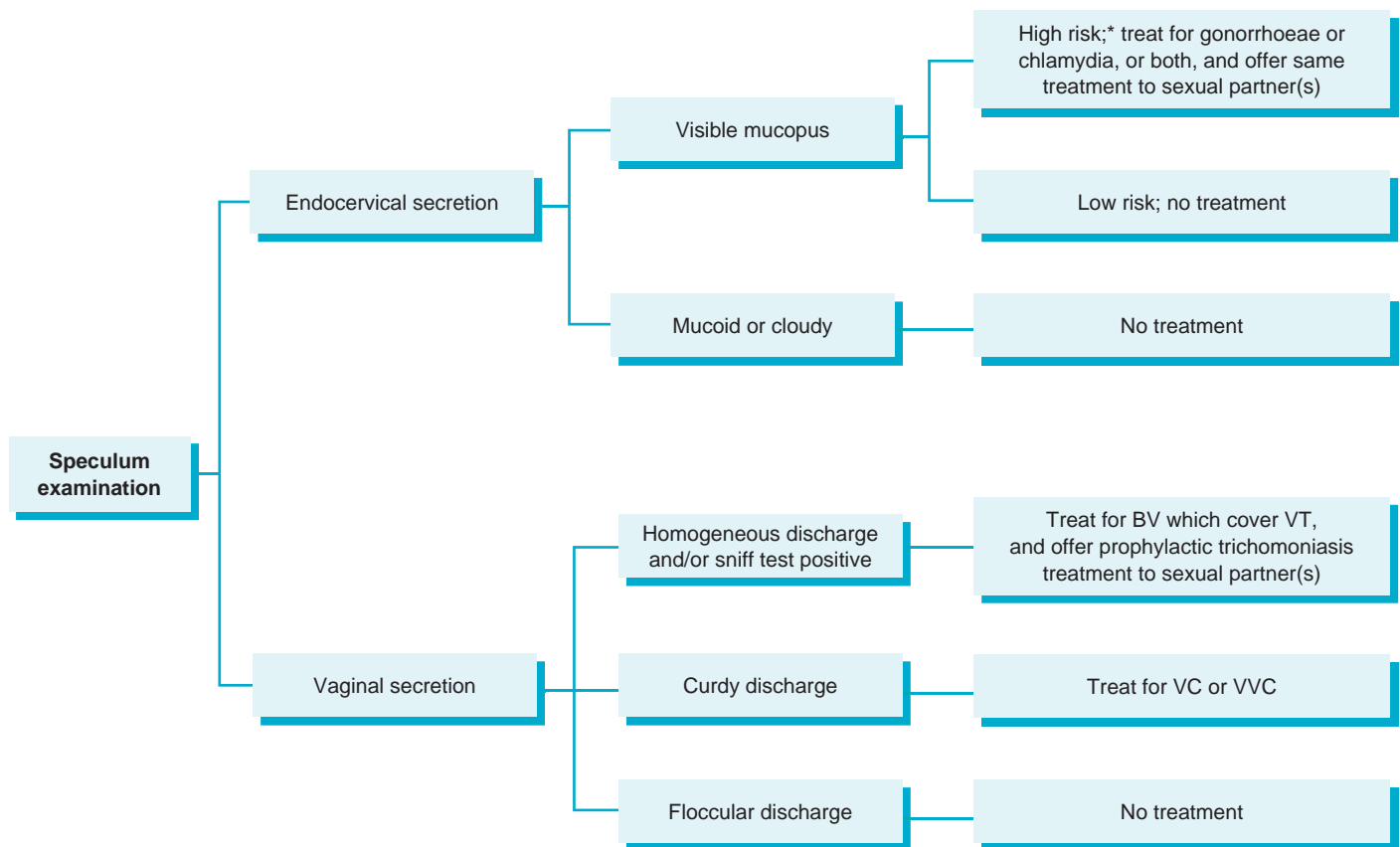
Dissolve 300 mg of methylene blue in 30 ml of ethanol. When the dye is dissolved, add 100 ml of distilled water. Mix the solution and sterilized by filtration (0.22 mm). Keep solution in darkness at 4°C until use.<sup>44</sup> Stain heat-fixed and air-dried smear with covering the slide by the stain for a few seconds. Wash slide under a running tap. Press a blotting paper against the slide and let dry before studying under oil immersion.

### Appearance of Vaginal Discharge

Vaginal secretion is collected from the lower speculum blade. Alternatively, a sterile cotton swab is inserted through the speculum and high vaginal specimen is taken. The characteristic features of the vaginal discharge can be classified into floccular (granular), homogeneous (milky), and curdy (cottage cheese-like) discharge. In pregnant women, the floccular and profuse discharge can be encountered (Figs. 56.2 a, b, c, and d). The sensitivity/specificity/positive predictive value/negative predictive value of characteristics of the discharge are: floccular for no vaginal infection 81/90/86/86%, homogeneous for BV 93/87/81/96, homogeneous for VT 100/59/10/100, homogeneous for BV or trichomoniasis 94/88/84/96%, and curdy for VC 72/100/100/93%, respectively.<sup>2</sup>

Based on macroscopic examination, the management flow chart of AVD can be planned (Fig. 56.3).

**Fig. 56.2:** The variety of vaginal discharge characteristics. (a) Floccular discharge. (b) Floccular and profuse discharge, usually in pregnant women. (c) Homogeneous discharge. (d) Curdy discharge.



\* High risk: prostitutes, persons with multiple sexual partners or a sexual partner with multiple sexual contacts, sexual contacts of persons with culture-proven sexually transmitted infection (STI), and persons with a history of repeated episodes of STI.

Fig. 56.3: Management flow chart of AVD: based on macroscopic examination.

## PERIPHERAL LABORATORY

Peripheral laboratory (simple office analysis) of vaginal secretion includes sniff test, amine test, pH paper test, wet mount preparation, and smear stain. Preceding the amine test, sniff test optionally performs to bypass the amine test in case of positive sniff test.

### Sniff Test

Inhalation of fishy odor, liberated from the speculum blade, is considered as positive sniff test.

### Amine Test

After specimen is taken for wet mount preparation, a drop of 10% KOH is added onto the discharge in the posterior blade of speculum. This is known as speculum amine test. The test is positive when fishy odor is released when a drop of 10% KOH is added onto the discharge in the microscopic slide. The glass slide amine test can be applicable, but less sensitivity.

The fishy odor results from the liberation of amines and organic acids produced by the alkalinization of anaerobic bacteria. A positive amine test is strongly suggestive of BV and VT.<sup>45</sup>

## pH Paper Test

The pH level can be measured by placing a drop of the discharge on a pH paper (short-range pH paper of pH 3.8–5.4, Merck), or whatever commercial pH papers. A high pH of more than 4.5 changes color of the paper from yellow or light green to dark green or deep blue. The result should be interpreted in the following manner: (i) pH 4.5 or less is suggestive of normal discharge or candidiasis; and (ii) pH more than 4.5 is likely to be due to BV or VT. Contamination with cervical mucus must be avoided, as the normal pH of cervical mucus is alkaline. The sensitivity/specificity/positive predictive value/negative predictive values of the pH of more than 4.5 for the diagnosis of BV are 95/72/67/96%.<sup>2</sup>

## Vaginal Wet Mount Preparation

From speculum, an appropriate amount of discharge is transferred separately at two different spots on the same slide for twin wet mount preparation. At one spot a droplet of normal saline is directly added for normal saline wet mount preparation. At the other spot 10% KOH solution is added for KOH wet mount preparation. Both the preparations are covered with a cover slip before immediate scanning under a light microscope. The



preparation should be examined at  $\times 100$  (low power) and then  $\times 400$  (high power) magnification. The substage condenser is kept down and the substage diaphragm is closed to increase the contrast.

The KOH promotes the cell lyses. Hyphae, filamentous elements with branching, are visible as clumps (Figs. 56.4 a and b). Experienced microscopist may occasionally detect budding forms. The detection of hyphae and mycelial filaments has sensitivity of 50–85%.<sup>19,46,47</sup>

Warming the KOH wet mount enhances the cell lysis. By this maneuver, filamentous elements become more clearly visible under microscope, but may lead to completely vaporized specimen.<sup>35</sup> Heat transfer to the site of normal saline wet mount preparation results in immovability of trichomonads. Wet mount preparation with 30% KOH should be avoided, as it also lyses the fungal element and eventually causes false-negative result.

Scanning of several fields for motile trichomonads has a sensitivity of 60–75% and a specificity of up to 99%.<sup>19,48</sup> Sending a “Hanging drop preparation” in 1 ml tube of normal saline solution to microscopic unit should be avoided because it greatly dilutes the concentration of vaginal materials and the collection-examination interval is prolonged. The sensitivity of trichomonad motility is affected in such a preparation. Some clinicians insist for hanging drop preparation; in that case, 0.25 ml saline solution in a tube is more preferable to increase the sensitivity.<sup>44</sup> Our experience

suggested that immediate examination yields results comparable with trichomonal isolation by Cyteine-Peptide-Liver-Maltose (CPLM) medium (unpublished observation).

Clue cell is a squamous epithelial cell with a fuzzy cytoplasm (like shading with black pencil), and cell border is indistinct or stippled rather than (normally seen) finely aligned (Figs. 56.5 a, b, c and d). This appearance is due to massive adherence by a set of BV organisms, *G. vaginalis* and anaerobic bacteria, onto the epithelial cell. If the number of clue cells is more than 20%, of total number of epithelial cells, a diagnosis of BV is suggested. Examination by wet mount preparations provides a sensitivity of 60% and a specificity of up to 98% for the detection of bacterial vaginosis.<sup>49–51</sup> The sensitivity/specificity/positive predictive value/negative predictive values of clue cells more than 20% for the diagnosis of BV are 81/99/97/90%.<sup>2</sup>

Quantitative assessment of lactobacilli is classified as predominant, scanty, or absence of large rod-shaped bacteria. Low number of lactobacilli is strongly suggestive of a diagnosis of BV. The sensitivity/specificity/positive predictive value/negative predictive value of scanty or absence of lactobacilli for the diagnosis of BV are 99/68/65/99%.<sup>2</sup>

These two diagnostic indicators (more than 20% clue cells and scanty or absence of lactobacilli) can be applicable to reproductive-age women but not the postmenopausal women, because of the physiologically decreased lactobacilli and squamous epithelial cell.

When clusters of BV organisms are discovered, they are called as “solid stage”.<sup>19</sup> This feature is seen either in postmenopausal or in reproductive-age. A diagnosis of atrophic vulvovaginitis is suggested if menopausal women have the urogenital symptoms and several signs of vulvovaginal atrophy along with an increased proportion of parabasal cell in wet mount preparation or cytological examination. The wet mount preparation also demonstrates PMN leukocytes and epithelial cells. Normally, the number of leukocytes is not more than epithelial cells. The PMN: epithelial cell ratio more than 1:1 could be either infective (e.g., MPC, VT) or non-infective condition (e.g., inflammatory and necrotizing process, late proliferative phase of the cycle). The sensitivity/specificity/positive predictive value/negative predictive values of PMN leukocytes: epithelial cell ratio more than 1:1 for the diagnosis of *N. gonorrhoeae* and *C. trachomatis* infections are 64/71/10/98%.<sup>2</sup>

### Vaginal Smear Stain

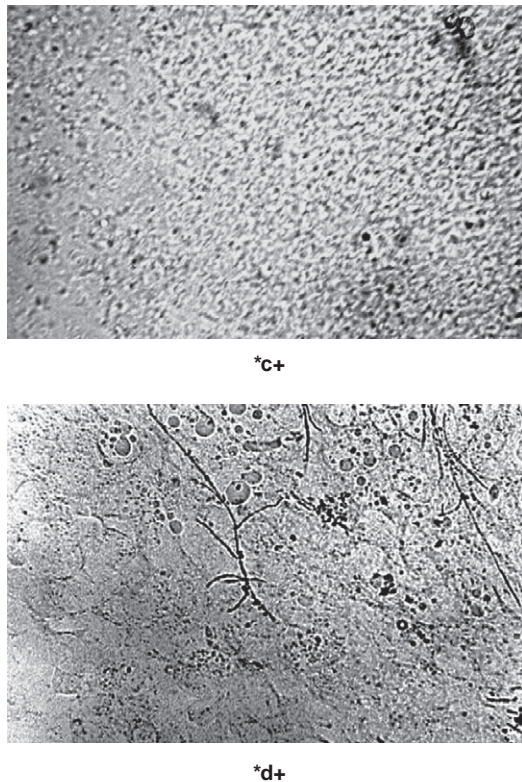
Vaginal smear stained with methylene blue, safranin, or Gram stain, can be used in place of the wet mount to detect predominant bacterial flora, clue cells, leukocytes, epithelial cell, and PMN: epithelial cell ratio, but not helpful for detecting trichomonads.

Based on macro/microscopic examination and peripheral laboratory, the management flow chart of AVD can be planned (Fig. 56.6).

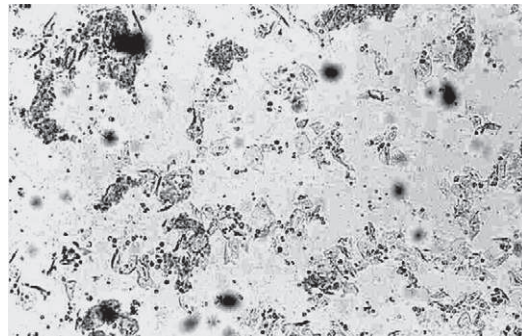
### Individual Entities

#### MUCOPURULENT CERVICITIS

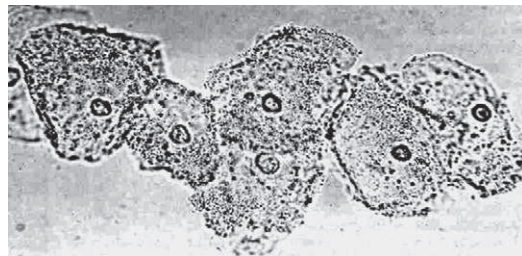
Trichomonad, *Candida*, and herpes simplex virus can cause inflammation of the ectocervix, ectocervicitis. Cervical



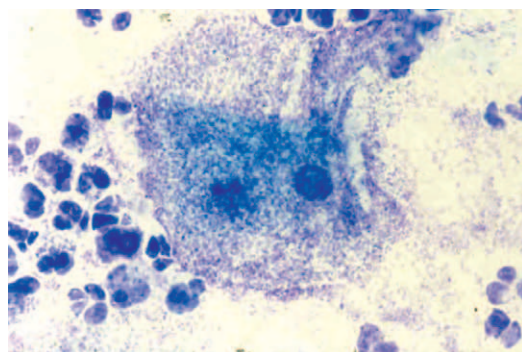
**Fig. 56.4:** KOH wet mount preparation (lower power field). (a) squamous vaginal epithelial cells, leukocytes, are lysed by 10% KOH and reveals clear cell background in the absence of hyphae. (b) hyphae (filamentous bodies) of *Candida*.



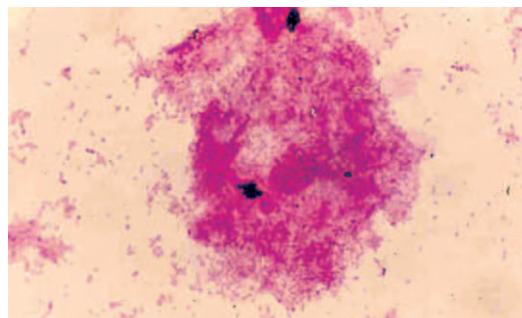
\*c+



\*d+



\*e+



\*f +

**Fig. 56.5:** Clue cells in various preparation. (a) Normal saline wet mount preparation (lower power field). (b) Normal saline wet mount preparation (high power field). (c) Methylene blue stain (oil field). (d) Safranin smear (oil field).

involvement of recurrent herpes apparently produces the multiple superficial ulcers. *N. gonorrhoeae* and *C. trachomatis* infect only the glandular epithelium, and are responsive for gonococcal and nongonococcal mucopurulent cervicitis (MPC).<sup>52</sup> Few studies,

*C. trachomatis* related to MPC has discovered in the range of 34.1–39%.<sup>53,54</sup> Roughly, at least one half of MPC is caused by *N. gonorrhoeae* and *C. trachomatis*.<sup>43</sup>

## Diagnosis

History of yellowish discharge is an indication toward the diagnosis of MPC. The diagnosis of MPC is based on clinical diagnostic criteria, of both visible mucopus and microscopic mucopus, the modified criteria.<sup>2</sup> Visible mucopus is considered when yellowish color is recognized on a white cotton-tipped swab, whereas, microscopic mucopus is reflected by the presence of 10 or more PMN leukocytes per oil field, at least five separate areas. MPC is disregarded and the patient needs to be re-evaluated if vaginal contamination in the specimen (Figs. 56.7 a and b). The vaginal contamination can be confirmed by: (i) more than 100 cells vaginal epithelial cells per slide, and (ii) vaginal flora more than 100 bacteria per oil field.<sup>43</sup> Positive identification of *N. gonorrhoeae* in smear or culture confirm gonococcal MPC. Nongonococcal MPC is classified into two categories depending on the chlamydial identification—chlamydia positive and chlamydia negative form.<sup>53</sup>

For MPC, the sensitivity/specificity/positive predictive value/negative predictive values of macroscopic and microscopic findings are as under: visible mucopus 36/86/11/97%, microscopic mucopus 64/69/9/98%, both visible and microscopic mucopus 36/87/12/97%, and visible or microscopic mucopus 64/71/10/98%, respectively.<sup>2</sup>

## Treatment

The therapy depends mainly on the isolation of the causative agent or clinical/microscopic findings. If *N. gonorrhoeae* is positive, a treatment regimen for uncomplicated gonorrhea (effective against penicillinase-producing *N. gonorrhoeae*) is recommended.<sup>55</sup> For nongonococcal MPC, either chlamydia positive or Chlamydia negative form, any regimen effective against *C. trachomatis* is preferable (Table 56.2). The same regimen should be prescribed to sexual partner(s). In pregnant women, MPC with negative identification of *N. gonorrhoeae* and *C. trachomatis* needs no treatment.

*C. trachomatis* probably co-infects with *N. gonorrhoeae*, and *vice versa*. Thus, epidemiological treatment of both organisms is considered in the areas of high prevalence of both pathogens.

In our experience, doxycycline, minocycline and ofloxacin are satisfactory for the treatment of MPC. In a trial with doxycycline (200 mg initially, followed by 100 mg twice daily for 8 days), the clinical assessment was satisfactory in 92.8%, the visible mucopus has disappeared in 86.8%, and the number of PMN leukocytes was reduced in 71.4% after completion of the treatment.<sup>56</sup>

Similarly, with minocycline (100 mg twice daily for 7 days), the clinical assessment was satisfactory in 94.8%, the visible mucopus has disappeared in 67.2%, and the number of PMN leukocytes was reduced in 51.7% after completion of the treatment. A wide variety of adverse drug events occurred; nausea, vomiting,



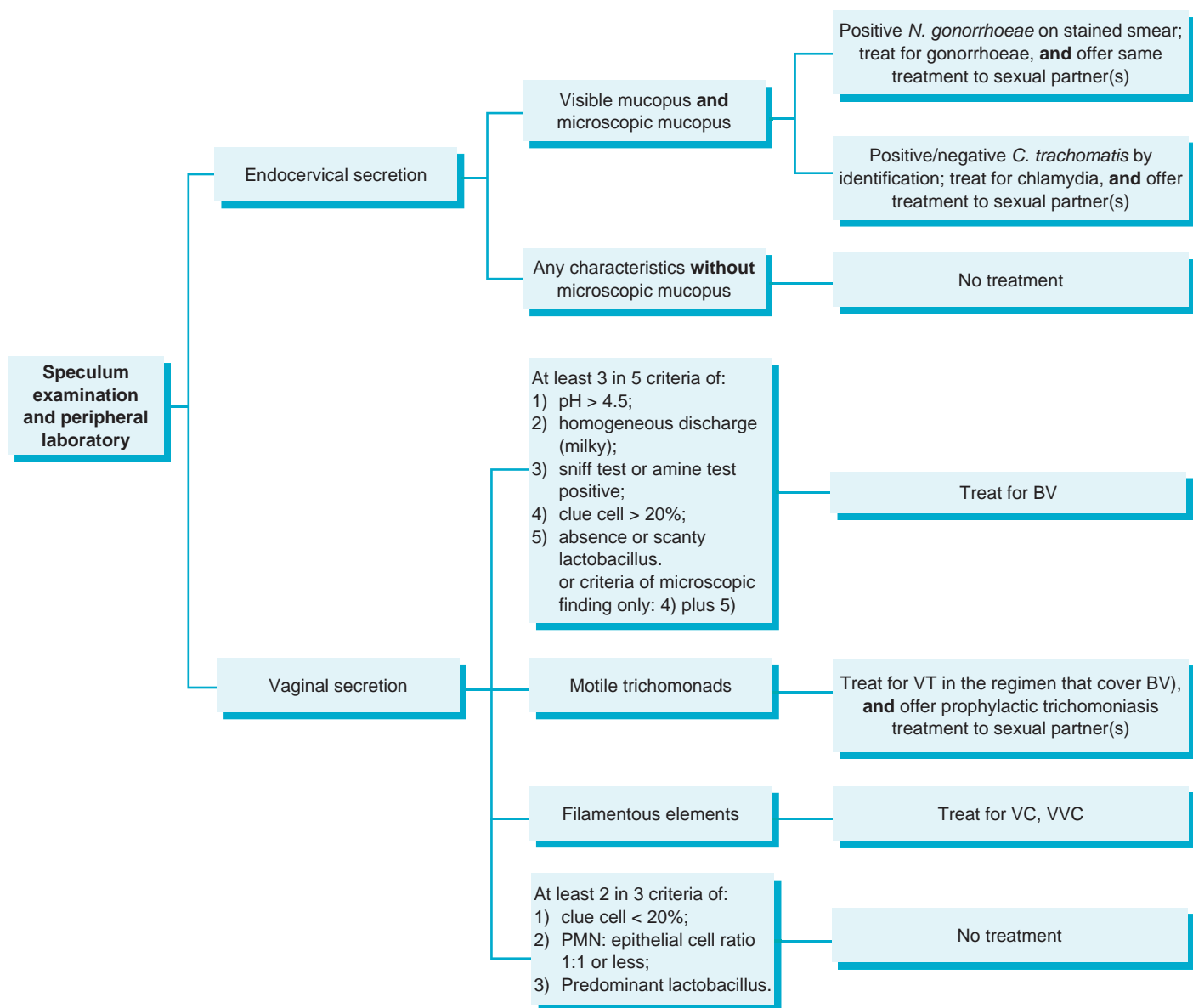
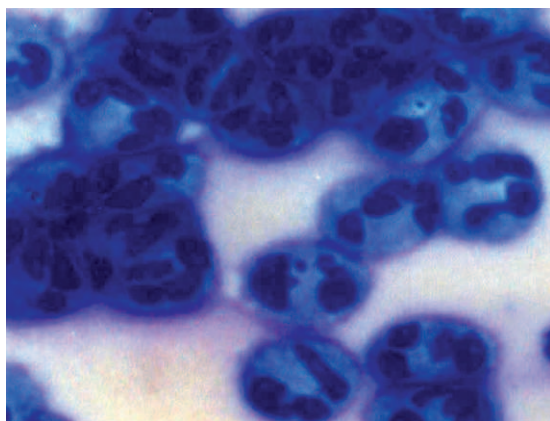
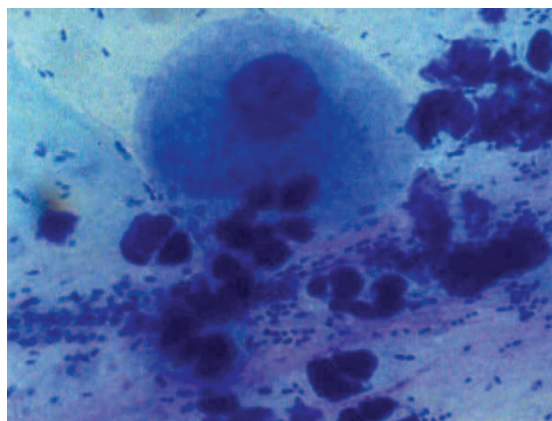


Fig. 56.6: Management flow chart of AVD: based on macro/micro examination and peripheral laboratory



\*c+



\*d+

Fig. 56.7: Methylene blue stain of endocervical smear ( $\times 1000$ ). (a) Microscopic mucopus; polymorphonuclear leukocytes more than 10 per oil immersion field in at least five representative areas, is diagnostic. (b) Heavy contamination by vaginal epithelial cells and flora is undesirable.



**Table 56.2:** Treatment of Gonococcal and Nongonococcal MPC

Disease	Regimens	
	Agent	Dosage
Gonococcal MPC	Ciprofloxacin*	500 mg orally in a single dose
	Ceftriaxone	250 mg intramuscularly in a single dose
	Cefixime	400 mg orally in a single dose
	Ofloxacin†	400 mg orally in a single dose
	Azithromycin*	2 g orally in a single dose
Nongonococcal MPC	Doxycycline*	100 mg orally twice daily for at least 7 days
	Minocycline†	100 mg orally once daily for at least 14 days
	Tetracycline†	500 mg orally, four times a day for at least 7 days
	Ofloxacin†	200–400 mg orally twice daily for at least 7 days
	Erythromycin stearate	500 mg orally, four times a day for at least 7 days
	Azithromycin*	1 g orally, single dose

\* Should only be given during pregnancy when need has been clearly identified.

† Established contraindication in pregnancy.

dizziness, and hyperpigmentation of oral mucosa.<sup>57</sup> When minocycline regimen was adjusted to 100 mg daily for 14 days, the clinical assessment was satisfactory in 91.4%, the visible mucopus has disappeared in 100%, and the number of PMN leukocytes was reduced in 85.7% after completion of the treatment. The adverse drug events were minimized.<sup>58</sup>

With ofloxacin (100 mg twice daily for 10 days), complete and partial responses are achieved in 66.7% and 27.8%, respectively of the patient with chlamydia positive MPC. This was not quite different from the patients with chlamydia negative form MPC with 68% complete and 32% partial response. Ofloxacin, 200 mg twice daily for 7 days produced comparable results.<sup>53</sup> Azithromycin, 1 g orally single dose can be considered as second line drug when the conventional treatments fail.<sup>55</sup>

Visible and microscopic mucopus in asymptomatic patients is apparently relates to the menstrual cycle. When AVD is relieved it is not necessary to provide the treatment to eradicate the mucopus, except when the upper genital tract infection is suspected. Uterine tenderness is suggestive of silent PID, while cervical and adnexal tenderness is correlated with overt PID. Further investigation includes endometrial sampling, clinical diagnostic criteria for PID, and eventually laparoscopy. Treatment of PID principally covers three main organisms, *N. gonorrhoeae*, *C. trachomatis*, and anaerobic bacteria.

Re-treatment for nongonococcal MPC is recommended if the test for cure reveals no response. When AVD persists without visible or microscopic mucopus, non-infective causes should be considered.

## BACTERIAL VAGINOSIS

Bacterial vaginosis (BV), formerly known as nonspecific vaginitis, has a poorly understood pathophysiology and is asymptomatic in up to 50% of women. Overgrowth of BV organisms results in the development of symptoms of excessive vaginal secretion and malodorous discharge. Many women complain of foul smell immediately after unprotected sexual intercourse. This is due to mixing of the discharge with alkaline semen, producing the aromatic amine.

## Diagnosis

Symptoms alone are not reliable for the diagnosis of BV. The diagnosis is based on a diagnostic criteria of clinical and laboratory indicators as follow:<sup>49,59</sup>

1. The vaginal pH greater than 4.5;
2. Homogeneous and thin discharge (milky discharge);
3. Positive sniff/amine test;
4. Clue cell greater than 20% of total vaginal epithelial cells;
5. Scanty or absence lactobacilli

Diagnosis of BV can be made if the patient fulfils 3 of 5 indicators.

One should be cautious that sexual intercourse within a few days can result in homogenous discharge, and seminal fluid may raise the vaginal pH to alkaline. In that case, the clinical diagnosis of BV should be made mainly on the basis of the wet mount preparation. The modified criteria of microscopic findings include the combined criteria of (i) clue cell greater than 20% of total vaginal epithelial cells; and (ii) scanty or absence lactobacilli. This can be applied in the settings that only microscopic examination is available.

BV needs to be treated only when the patient fulfills of diagnostic criteria. The issue regarding treatment of asymptomatic cases or low-risk pregnant women with BV remains unresolved. The secondary preventive screening and treatment of both symptomatic and asymptomatic cases of BV before reproductive tract surgery is recommended.

## Treatment

Erythromycin and doxycycline have not been found effective for treatment of BV.<sup>60,61</sup> Metronidazole and other 5' nitroimidazoles are effective drugs in treatment of BV. Treatment of male sex partner(s) with metronidazole has no benefit in the preventing of recurrent BV.<sup>62</sup> The facultative flora of vagina, Lactobacilli are resistant to metronidazole. VC may develop in only a small numbers of women treated with metronidazole. Metronidazole has been found to be carcinogenic in rodents. The efficacy of metronidazole must be weighed against its potential toxicity. It must be avoided in pregnant women, especially in first trimester.

Metronidazole, 500 mg orally twice daily for 7 days, has cure rates for BV in the range of 92–100%.<sup>63–65</sup> Two grams of

tinidazole, a double dose of 48 hours apart, has produced cure in about.<sup>65</sup> In another study, nimorazole 500 mg orally twice daily for 7 days, cured about 90%.<sup>59</sup> Clindamycin, 300 mg orally twice daily for 7 days, produced complete response in 94.5%, and partial response in 5.5%.<sup>66</sup>

In summary, oral metronidazole is a preferable treatment for BV with dramatic response. Other effective agents include tinidazole, nimorazole, and clindamycin, can be used if the patient is unable to tolerate metronidazole. Complete response to treatment often rules out drug resistance. If the first test of cure reveals partial response or no response, possibility of resistance and persistence of infection should be considered. Such patients should be treated with antimicrobial agent of a different group.

### VAGINAL AND VULVOVAGINAL CANDIDIASIS

Genital infection with *Candida* can result in either vaginal candidiasis (VC) or vulvovaginal candidiasis (VVC). More than 50% of women older than 25 years, have had one episode of vulvovaginal candidiasis,<sup>67</sup> but fewer than 5% of these women experience recurrent infection.<sup>68</sup> Generally, *Candida* is not transmitted sexually and episodes of VC/VVC seem unrelated to the number of sexual partners.<sup>68,69</sup> Treating the male partner is unnecessary unless he has balanitis and balanoposthitis.<sup>9</sup>

VC/VVC occurs more frequently in pregnant women, and its incidence increases with gestational age. It usually does not pose serious problems to the mother and the newborn, although the symptoms can be distressing. The disease in mother often clears up spontaneously after delivery. Women with VC/VVC may be asymptomatic or may present with complaints of mild to severe degree of itching, discharge, pain, swelling, erythema, edema, and ulceration. The most severe infection often occurs in pregnant women who are diabetics.

### Diagnosis

Examination demonstrates erythema, inflammation, and an adherent discharge described as “cottage cheese-like”. Establishing *Candida* species as the cause of organisms is difficult, because as many as 50% of asymptomatic women, as part of their endogenous vaginal flora.<sup>68</sup> So, the diagnosis of VC is established only when hyphae are detected on KOH wet mount preparation. Other characteristics suggesting VC include a vaginal pH less than 4.5 and a lack of odor in the discharge.

There is evidence that the inflammation of VC is immunologically mediated as in symptomatic women, only small numbers of fungus is present.<sup>70</sup> The diagnosis of VC should never be made when hyphae are absent. Isolation of *Candida* through culture can be undertaken in patient with no demonstrable hyphae but presence of mixed clinical symptoms such pruritus, erythematous vulvar rash, vulvar fissure, or white vulvar plaque.<sup>71</sup> Occasionally, yeast forms can be detected by Papanicolaou smear or fungal isolation. It is not necessary to treat the yeast form. In

those cases but the hyphae do. In those cases, the patient should be re-evaluated. When the KOH wet mount preparation reveals hyphae element, therefore, VC/VVC treatment is indicated.

### Treatment

Topical polyene such as nystatin, 100,000 units, intravaginally daily is well-tolerated and inexpensive, but requires continuous therapy for 2 weeks, which may affect patient compliance. The cure rate is in the range of 50–80%.<sup>9</sup> Topical polyenes have been largely replaced by topical azoles, in the treatment of VC even in the pregnant women, as first-line drug. Now, topical and oral azoles are available in a variety of formulations. The average cure rate of topical azoles is in the range of 80–90%. Oral azoles achieve comparable or marginally higher therapeutic cure.<sup>19,72</sup> The oral agents, however, do not provide immediate relief of local symptoms, hence severe vulvar symptoms may necessitate adjunct topical treatment for the first few days.

After adequate the local therapy azole, persistent infection is considered, if the first test of cure reveals partial response or no response suggested by detection of hyphae. In such patients re-treatment should be considered either different local therapy with a different azole, or the combination of local and oral azoles, as the second-line therapy.

Recurrent VC/VVC is distinguished from persistent infection by the presence of a symptom-free and pathogen-free interval. Recurrent VC is considered when, following complete response, at least three episodes unrelated to antibiotic therapy occur within one year.<sup>73</sup>

In the patient with recurrent infections, the risk factors should be eliminated. In VC/VVC recurring after complete cure with adequate treatment, prophylactic therapy should be initiated. A short course of local or oral azole for 5 or 6 days, is administered in the week before next cycle of menstruation for three consecutive cycles is an effective prophylactic regimen to reduce the rate of recurrence. If necessary, the isolation of *Candida* through culture may be helpful in identify other less common species of *Candida*.

### VAGINAL TRICHOMONIASIS

A strawberry cervix, demonstrating typical epithelial hemorrhages is considered as a presumptive diagnosis of vaginal trichomoniasis (VT), however this characteristic sign is seen only in about 2% of the patients with VT.<sup>74</sup> Strawberry cervix is a sign of advanced trichomoniasis, hence is becoming rarer in the present era due to early diagnosis and treatment.

### Diagnosis

The presence of *T. vaginalis* correlates poorly with symptoms and signs in women,<sup>75,76</sup> the diagnosis of trichomoniasis, therefore, depends on detection of motile protozoan (Figs. 56.8 a and b). BV always coexists with VT infection. On the other hand, VT co-infection with VC is rare, only in optimized vaginal pH

conditions. VT is considered as a STI, although only about 30% of male sexual partners of infected women have positive urine isolation. Most men are asymptomatic.<sup>77</sup>

## Treatment

Women with VT can be treated with metronidazole 2 g given orally as single dose, along with treatment of partner(s) in the same dose. This regimen is moderately effective with cure rates in the range of 82–88%.<sup>78</sup> More preferable regimen is metronidazole 500 mg orally twice daily for 7 days, along with treatment of partner(s) with 2 g orally.<sup>2,79</sup> This regimen not only provides higher cure rates, but also cure concomitant BV. Optionally, other 5' nitroimidazoles can also be applied.

Metronidazole, like disulfiram, blocks hepatic metabolism of ethanol to aldehyde intermediaries, which produce a variety of systemic symptoms including nausea and flushing. Patients should be cautioned about consumption of alcohol while on treatment. According to a recent meta-analysis, the single 2 g dose of oral metronidazole can be used safely in any trimester of pregnancy.<sup>80</sup>

The test of cure is recommended in every case to make clear whether the result of the treatment is complete, partial or no response. Recovery of pathogen and diagnostic criteria after completion of

therapy is considered as either re-infection from the partner(s) or failure of the therapy. To achieve the complete response, the management includes partner's assessment and re-treatment with and other 5' nitroimidazoles. If this also fails, then the combination of vaginal and oral 5' nitroimidazoles are recommended.<sup>81</sup>

## NON-INFECTIVE LEUKORRHEA

Most infectious causes may be included or excluded by standard basic investigation. Non-infective leukorrhea (NIL) should be considered as the diagnosis in women with AVD when following criteria are fulfilled:<sup>2</sup>

### Endocervical secretions

- Absence of visible mucopus,
- Absence of microscopic mucopus,

### Vaginal secretion

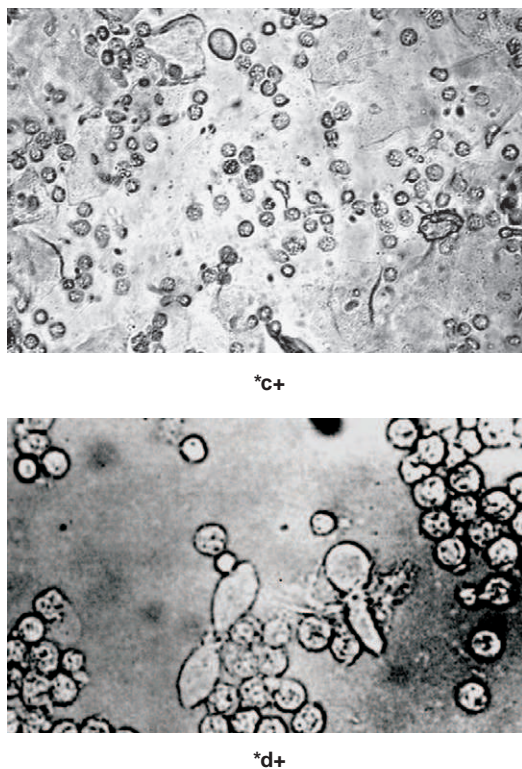
- Absence of trichomonad motility,
- Absence of filamentous elements,
- Clue cell less than 20% of total vaginal epithelial cells,
- Numerous lactobacilli,
- PMN leukocytes: epithelial cell ratio is 1:1 or less

If all seven criteria are fulfilled, vaginal and cervical infections can be safely excluded.<sup>2</sup> In NIL, the striking microscopic findings in vaginal secretion are of an abundance of large rods and normal vaginal epithelial cells (Figs. 56.9 a and b). The coincident findings include a small number of leukocytes and clue cells less than 20% of total vaginal epithelial cells. Other suggestive findings are absence of both trichomonad motility and hyphae. Cervix does not show visible or microscopic mucopus.

Women with prominent discharge with no any abnormal findings on basic investigation should be considered to be cases of NIL. The perineal hygiene care should be strongly advised to practice. With this, AVD is relieved or alleviated in majority of the cases. In a study of 70 patients with NIL, 48 (68.5%) improved with perineal hygiene care, while, 22 (31.4%) persisted of excessive vaginal secretion and/or yellowish discharge. Among 22 patients with persistent AVD, test of cure was categorized. First group of 12 (54.5%) patients had persistent NIL. These patients were evaluated for other non-infective causes responsible for altered vaginal flora, and physiologically changes. These conditions include smegma reaction, reaction to barrier contraceptives, vaginal douches, sexual arousal, pattern of sexual practices, and change of sexual partner(s), etc. Second group of 9 in 22 (40.9%) patients comprised of 1 case with MPC and 8 cases with either visible or microscopic mucopus. MPC case requires re-evaluation and re-treatment, while the remaining 8 cases needed further evaluation and investigations. Third group of 1 (4.5%) patient had late development of BV, treated accordingly.<sup>2</sup>

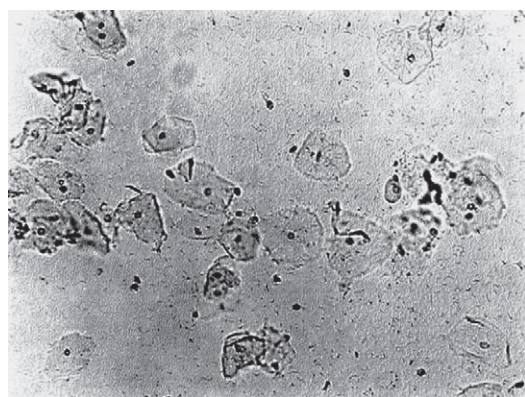
## Perineal Hygiene Care

The female sex organs are more complex than those of the male. The location of external urethral meatus, introitus of the vagina, and the opening of anal, are adjacent to each other and this may result in

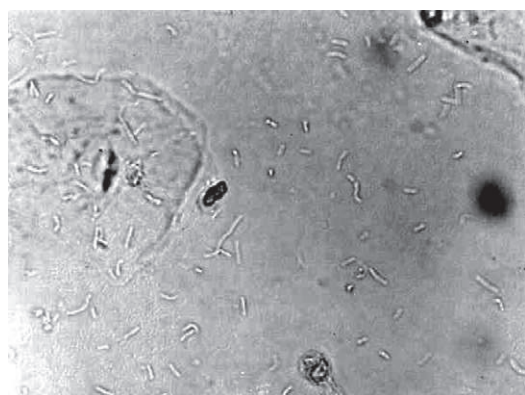


**Fig. 56.8:** Normal saline wet mount preparation. (a) Squamous vaginal epithelial cells, numerous leukocytes, ovoid body slightly larger than leukocyte (lower power field). (b) Ovoid body of trichomonads (high power field), motility is suggestive of trichomoniasis.





\*c+



\*d+

**Fig. 56.9:** Normal saline wet mount preparation. (a) Squamous vaginal epithelial cells (intermediate cell), and numerous lactobacilli (lower power field). (b) Squamous vaginal epithelial cell, and numerous of thin rods (high power field).

a vaginal ecosystem contaminated with bacteria mainly from feces and urine. Cleanliness around the external genitalia is important. Following instructions should be given to the patients: when there is an infection resulted from lower genital tract, to avoid the change of vaginal ecosystem. Suggestions for practice are as follow:<sup>34</sup>

- After bath, defecation, and sexual intercourse, always wash the area with water and dry it thoroughly before putting on underwear.
- After defecation, wipe and wash from front to back (from vagina to anus) to avoid fecal contamination of vagina.
- In hot weather causing too much perspiration, the underwear should be changed more frequently. A wet underwear produces smell and itching. An irresistible urge to scratch can in turn cause rashes and abrasion.
- Avoid wearing nylon and rayon underwear, as they cause more sweating than cotton underwear. The underwear with cotton component at least 60–80% is suggested, especially those allergic to synthetic materials.
- The underwear should be sun or heat-dried to remove all the moisture.

- In some circumstances soft stool may stain the underwear. In that case, the underwear should be changed immediately.
- The vagina should not be spray-washed. It may carry bacteria from the vagina into the intrauterine cavity. If necessary, the vagina can be cleaned with fingers. The fingernails should be kept trimmed to avoid risk of trauma.
- Vaginal douching with antiseptics is unnecessary and it may damage the vaginal epithelium. At times, patient may be allergic to the antiseptics.
- The tampon should be changed frequently. When the diaphragm is used, it should not be left in the vagina longer than the recommended period.

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## Introduction

The symptom of lower abdominal pain in women is a common one and may occur in a large number of conditions including disorders of the bladder, bowel, musculoskeletal system, and the female reproductive organs.

An important cause of lower abdominal pain in women is pelvic inflammatory disease (PID). PID is defined as infection of the female genital tract above the internal os of the cervix. This implies endometritis, salpingitis, salpingo-oophoritis, tubo-ovarian abscess, and pelvic peritonitis. PID is caused by bacterial infection ascending from the cervix. The bacterial pathogens that cause PID are *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and anaerobic and aerobic bacteria.<sup>1,2</sup> The majority of women with gonococcal or chlamydial infection of the cervix have no symptoms at all. When symptoms do occur, they may be related to complications such as PID. PID is an important health problem, as it can lead to death as a result of ruptured pelvic abscess, pelvic peritonitis, and ruptured ectopic pregnancy, and it can lead to sub-fertility or infertility.<sup>1</sup>

Women with PID usually present with lower abdominal pain, but this is a common symptom and not all women with lower abdominal pain have PID. Women with other potentially life-threatening conditions such as ectopic pregnancy, appendicitis, pelvic abscess or complications of pregnancy such as incomplete abortion, septic incomplete abortion, and puerperal sepsis may also present with lower abdominal pain. Women with PID may also have other symptoms such as menstrual problems, vaginal discharge, dyspareunia, fever, diarrhea, and even vomiting.<sup>3-5</sup>

In order to make a diagnosis of PID, a detailed history should be taken and the patient should be examined carefully. From the history and examination, it is possible to identify those women with lower abdominal pain who may have a surgical or obstetric complication requiring immediate referral to a hospital for specialist attention. The following symptoms and signs are suggestive of PID:

- History of lower abdominal pain, vaginal discharge, irregular menstruation, and fever.
- Pain and tenderness in the pelvis detected on abdominal palpation.

- Cervical excitation tenderness detected by digital vaginal examination.
- Depending on the severity of the condition, signs of septicemia may also be present, and the patient may be extremely ill and toxic.

## Clinical Criteria for Referring Women with Lower Abdominal Pain for Specialist Attention

Since lower abdominal pain in women may be caused by a large number of conditions, it is important that a thorough assessment be carried out so that patients with serious conditions and complications are provided with adequate care, including referral for specialist opinion. The following features in the history are indicative of a gynecologic problem requiring immediate gynecologic attention<sup>6</sup>:

- History of a missed or delayed period, or that a period is overdue—this is suggestive of a pregnancy complication or ectopic pregnancy.
- History of abortion within the preceding 6 weeks suggestive of incomplete abortion or septic incomplete abortion.
- History of a delivery or miscarriage within the preceding 6 weeks—suggestive of a complication following parturition, such as retained products of conception or pelvic sepsis.
- History of irregular heavy vaginal bleeding—suggestive of incomplete abortion, retained products of conception or placental tissue, or dysfunctional uterine bleeding.

From the examination, the following features are indicative of a surgical or gynecologic complication requiring specialist opinion:

- Abdominal guarding and rebound tenderness—suggestive of peritonitis, intra-abdominal bleeding, or intra-abdominal abscess.
- On abdominal palpation, a mass is found—suggestive of an abscess, ovarian cyst, fibroid, or tumor.
- Active heavy continuous vaginal bleeding—suggestive of a pregnancy complication.

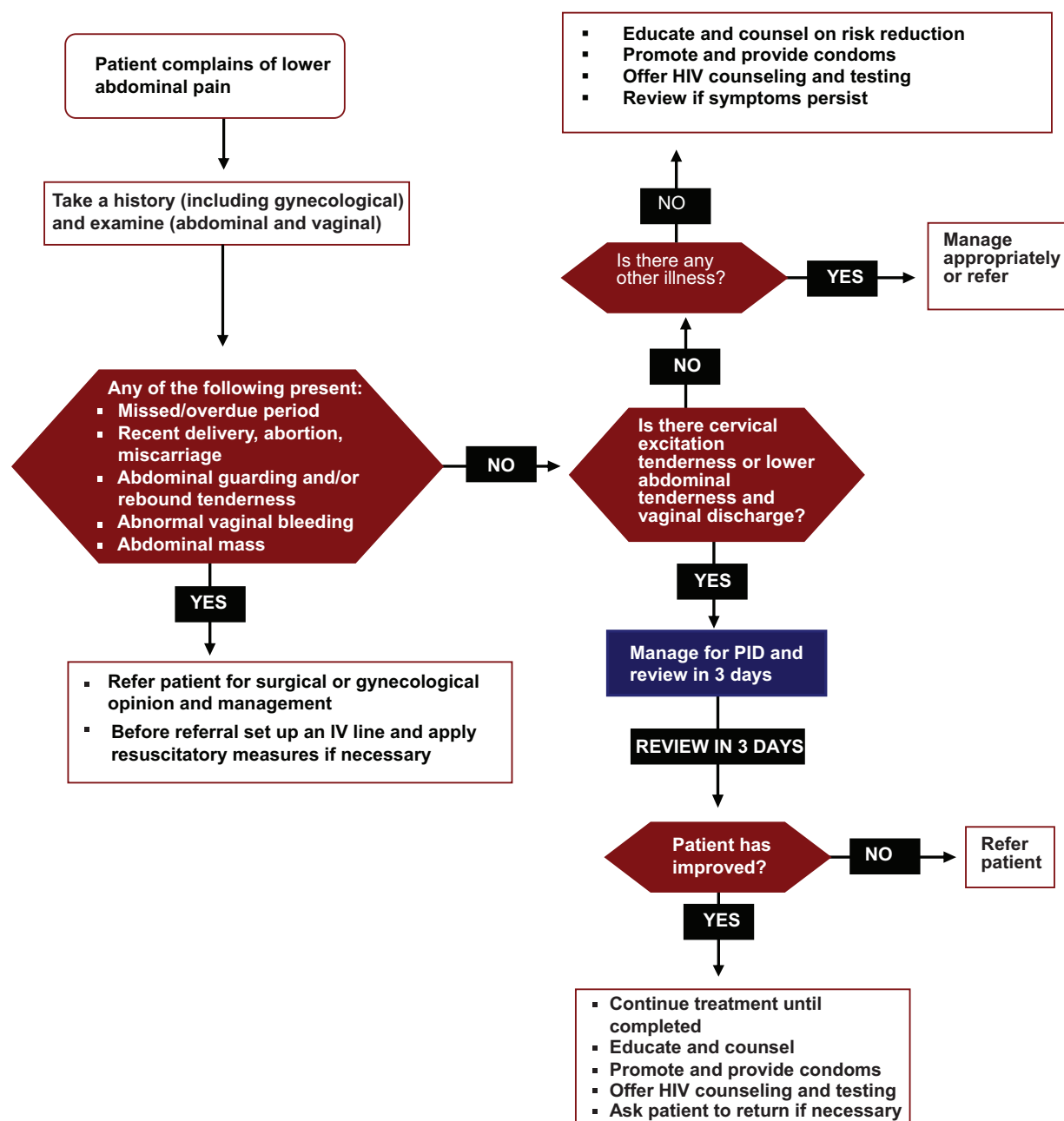
**Table 57.1:** Symptoms and Signs Indicative of a Surgical or Gynecological Problem Requiring Immediate Referral for Specialist Attention

Symptoms	Signs
Missed, overdue, delayed period	Abdominal guarding and/or rebound tenderness
Recent abortion, delivery or miscarriage	Abdominal mass
Metrorrhagia	Active vaginal bleeding

Table 57.1 summarizes the referral criteria for women with lower abdominal pain.

### Management of Lower Abdominal Pain in Women

As the main causes of PID include gonococcal, chlamydial, and anaerobic bacterial infection, all women who have PID should be treated for these infections initially. The flowchart in Figure 57.1 gives guidance on the syndromic management

**Fig. 57.1:** Flowchart for the management of lower abdominal pain in women.

of lower abdominal pain in women. The flowchart may be summarized as follows:

- In all women with lower abdominal pain, a history should be taken and a careful examination should be carried out.
- From the history, the following information should be obtained: has the patient missed a period, has there been a delayed period, or has a period been overdue, is there a history of an abortion or delivery in the preceding six weeks; or is there a history of irregular heavy vaginal bleeding.
- When examining the patient, look specifically for the following:
  - Is there abdominal guarding or rebound tenderness?
  - Is a mass palpable in the abdomen?
  - Is there vaginal bleeding?
- If none of the above referral criteria are present and the patient has vaginal discharge and/or cervical excitation tenderness, then the most likely diagnosis is PID. This patient must be treated for PID as described below and should be reviewed in 3 days time or sooner if symptoms are not improving or if she is feeling worse. On review in 3 days if she is improving then continue treatment for a total of 14 days.

## Treatment of PID

The patient with PID should be treated for gonococcal, chlamydial, and anaerobic bacterial infection. The following recommendations are made: All patients should be treated for gonococcal, chlamydial, and anaerobic bacterial infections. Patients treated on an outpatient basis should be reviewed 72 hours after starting treatment or sooner if their symptoms become worse. At the 72-hour review, if patients are not improving then they should be referred for specialist (surgical or gynecological) opinion. If they are improving, then treatment should be continued for a total of 14 days. Intrauterine contraceptive devices should be removed after starting therapy.

### TREATMENT ON AN OUTPATIENT BASIS (Box 57.1)

- Single-dose therapy for uncomplicated gonorrhea (i.e., ceftriaxone 250 mg IM or ciprofloxacin\* 500 mg PO), PLUS
- Treatment for chlamydial infection with doxycycline 100 mg orally twice daily for 14 days, PLUS
- Treatment for anaerobic bacterial infection with metronidazole, 500 mg orally, twice daily for 14 days.

#### Box 57.1 Outpatient Therapy for Pelvic Inflammatory Disease

- Ceftriaxone 250 mg IM OR Ciprofloxacin\* 500 mg by single oral dose, PLUS
- Doxycycline 100 mg orally twice daily for 14 days, PLUS
- Metronidazole 500 mg orally twice daily for 14 days

**Note:** Review the patient in 72 hours after starting treatment and if she has improved continue treatment; if she has not improved refer her to a health facility where specialist surgical and gynecological opinion may be obtained.

\*Quinolones are no longer recommended for gonococcal infection in Asia.

Review the patient in 72 hours time and refer her if she is not improving or continue treatment if she is improving.

#### Notes:

1. Patients taking metronidazole should avoid taking alcohol.
2. Ciprofloxacin and other quinolones are no longer recommended for treatment of gonorrhoea in Asia. Quinolones are contraindicated during pregnancy and lactation.
3. The intrauterine contraceptive device (IUCD) is a possible risk factor for the development of PID. It is recommended that the IUCD be removed soon after antimicrobial therapy for PID is commenced. When an IUCD is removed, contraceptive counselling is necessary.
4. All patients treated on an outpatient basis should be reviewed 72 hours after commencing treatment. If the patient is not improving, then she should be admitted or referred for admission and for specialist opinion and management.

### INPATIENT TREATMENT (Box 57.2)

Acute PID may be a life-threatening condition, as it can lead to the development of intra-abdominal abscesses and peritonitis. Patients may develop septicemia and septic shock. Bowel fistulae are also known to occur during this time. Therefore, women who have PID and also signs of tubo-ovarian abscess or pelvic and generalized peritonitis need to be referred for inpatient management. In addition, women with lower abdominal pain in whom a surgical cause cannot be ruled out and women in whom a complication of pregnancy such as, threatened, incomplete or septic abortion, and retained products of conception, need to be referred for specialist opinion.

For patients hospitalized with acute PID, any of the following three regimens may be used:

#### Regimen 1:

- Treatment for gonococcal infection with ceftriaxone 250 mg intramuscular daily for at least 2 days after the patient has improved, PLUS
- Treatment for chlamydial infection with doxycycline, 100 mg orally twice daily, or tetracycline, 500 mg orally, 4 times daily for 14 days, PLUS
- Treatment for anaerobic bacterial infection with metronidazole, 400 mg (or 500 mg) orally, twice daily for 14 days.

#### Regimen 2:

- Clindamycin 900 mg IV every 8 hours for at least 2 days after the patient has improved, PLUS
- Gentamicin 1.5 mg/kg IV 8 hourly for at least 2 days after the patient has improved, FOLLOWED BY
- Doxycycline 100 mg orally twice daily or tetracycline 500 mg orally 4 times daily for 14 days, AND
- Metronidazole 500 mg orally or by intravenous injection, twice daily for 14 days.

#### Regimen 3:

- Ciprofloxacin\* 500 mg orally twice daily for at least 2 days after the patient has improved, PLUS
- Doxycycline 100 mg orally twice daily or tetracycline 500 mg orally 4 times daily for 14 days, PLUS



**Box 57.2** Inpatient Therapy for Pelvic Inflammatory Disease**Regimen 1:**

- Ceftriaxone 250 mg by intramuscular injection daily for at least two days AFTER the patient has improved, PLUS,
- Doxycycline 100 mg orally twice daily for 14 days (or, Tetracycline 500 mg orally 4 times a day for 14 days), PLUS,
- Metronidazole 400 mg (or 500 mg) orally twice daily for 14 days

**Regimen 2:**

- Clindamycin 900 mg by intravenous injection every 8 hours for at least 2 days AFTER the patient has improved, PLUS,
- Gentamicin 1.5 mg/kg intravenously every 8 hours for at least 2 days AFTER the patient has improved FOLLOWED BY
- Doxycycline 100 mg orally twice daily for 14 days (or, Tetracycline 500 mg orally 4 times a day for 14 days), PLUS
- Metronidazole 400 mg (or 500 mg) orally twice daily for 14 days

**Regimen 3:**

- Ciprofloxacin 500 mg orally twice daily for at least 2 days AFTER the patient has improved, PLUS,
- Doxycycline, 100 mg orally twice daily, or tetracycline, 500 mg orally, 4 times daily for 14 days, PLUS,
- Metronidazole 400 mg (or 500 mg) orally or by intravenous injection, twice daily, OR,
- Chloramphenicol, 500 mg orally or intravenously injection, 4 times daily

- Metronidazole 400 mg (or 500 mg) orally or by intravenous injection, twice daily.

**Notes:**

1. Patients taking metronidazole should avoid taking alcohol
2. The intrauterine contraceptive device (IUCD) is a possible risk factor for the development of PID. It is recommended that the IUCD be removed soon after antimicrobial therapy for PID is commenced. When an IUCD is removed contraceptive counselling is necessary.
3. Ciprofloxacin is contraindicated in pregnancy and not recommended in infections acquired in Asia.

**Conclusion**

Pelvic inflammatory disease is a serious complication of STIs. Women with PID usually present with lower abdominal pain. The symptoms of lower abdominal pain do not always indicate that the patient has PID and hence, other conditions should always be looked for and excluded. Lower abdominal pain also occurs in surgical and gynecologic conditions, and these conditions should be excluded by taking a history and by carrying out a careful

examination. It is best to refer all women with lower abdominal pain who give a history of any one or more of the following:

- Missed, overdue, or delayed period
- Recent abortion, delivery, or miscarriage
- Irregular and continuous vaginal bleeding

Also refer all women with lower abdominal pain in whom an examination reveals any one or more of the following:

- Abdominal guarding or rebound tenderness
- Abdominal mass
- Vaginal bleeding

**Summary**

The symptom of lower abdominal pain in women is extremely common and does not always indicate the presence of serious illness. However, women with certain serious conditions such as pelvic inflammatory disease (PID), acute appendicitis, ectopic pregnancy, and other complications of pregnancy may present initially with this symptom as well. Therefore, in managing women with lower abdominal pain care should be taken to exclude any serious condition before dismissing the symptoms of patient. PID is a condition in which there is infection in the female reproductive tract above the internal os of the cervix. This usually occurs as a result of an ascending cervical infection caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, anaerobic bacteria and other pyogenic bacteria. The immediate and long-term effects of PID include salpingitis, pelvic abscess, peritonitis, infertility, and predisposition to tubal ectopic pregnancy. Women with lower abdominal pain should be assessed carefully; if PID is the cause, they should be treated for gonococcal, chlamydial, and anaerobic bacterial infection. Other gynecological and surgical causes of lower abdominal pain and the immediate complications of PID require urgent referral to a specialist. PID is associated with significant morbidity and mortality.

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## Introduction

Historically, Hippocrates first described that certain genital ulcers are accompanied by swellings in the groin, which were later termed as buboes.<sup>1</sup> Inguinal and femoral buboes are defined as the localized enlargement of the lymph nodes in the groin area that are painful and may or may not be fluctuant.<sup>2</sup>

## Etiology and Epidemiology

The most common causes of inguinal and/or femoral buboes are infection with *Haemophilus ducreyi*, the causative organism of chancroid, and *Chlamydia trachomatis*, L1-L3 strains, which cause lymphogranuloma venereum (LGV). A Thai study has shown that there is no role of other aerobic and anaerobic bacteria in the development of buboes associated with chancroid and LGV.<sup>3</sup> However, others have frequently isolated anaerobes from fluctuant chancroidal buboes.<sup>4,5</sup> Both chancroid and LGV are rare diseases even in tropical and subtropical regions. A recent review of sentinel surveillance of STIs in South Africa has shown that chancroid and LGV have declined considerably, which is attributed to implementation of syndromic management since 1994.<sup>6</sup> O'Farrell et al.<sup>7</sup> reported that among 162 patients with genital ulcers presented at an STI clinic in Durban between January and March 2004, 13.6% had LGV and 1.2% had chancroid. The cases were diagnosed by polymerase chain reaction (PCR). Data from an STD clinic in New Delhi, India, showed that during 1990–1993 chancroid constituted 21.3% of all genital ulcers in men, while during 2002–2004 only 6.9% of all men with genital ulcers had chancroid.<sup>8</sup> Corresponding figures for LGV for these periods were 5.7% and 0.4%, respectively.<sup>8</sup> In the 21 Century, it is still rarer to see the classical presentation of LGV with inguinal bubo. Since 2003 there has been a resurgence of LGV in western Europe, United States, and Australia in HIV positive MSM population; however, it is in the form of LGV proctitis rather than classical inguinal syndrome.<sup>9,10</sup> However, Sethi et al.<sup>11</sup> recently reported a series of classical inguinal syndrome from United Kingdom in HIV positive MSM population.

It is common to see inguinal suppuration as a complication of several other diseases. These include pyogenic infection of the leg, cat-scratch disease,<sup>12</sup> tuberculosis,<sup>13</sup> plague, and guinea worm infestation.<sup>14</sup> Secondary bacterial infection in the genital lesions of scabies and pediculosis pubis may result in tender inguinal lymphadenopathy (Fig. 58.1). Secondary bacterial infection in primary syphilitic chancre can also give rise to inguinal bubo (Fig. 58.2), which may suppurate if not treated. Atypical mycobacteria, like *Mycobacterium avium-intracellulare* and *Mycobacterium chelonae* have been reported to cause inguinal abscesses.<sup>15,16</sup> In many patients with inguinal bubo, no cause can be determined.<sup>3,17</sup> Some of these patients receive empirical antibiotic treatment before they report to the physician, making it difficult to isolate the pathogen. Nevertheless, a majority of such patients would respond to treatment regimens recommended for the management of inguinal buboes.<sup>3</sup>

## Clinical Features

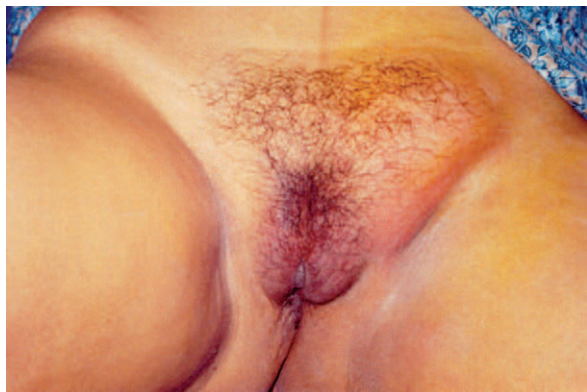
About 50% of patients with chancroid develop buboes.<sup>18</sup> The buboes associated with chancroid are usually unilateral and are more prevalent in men than in women (Figs. 58.3



**Fig. 58.1:** Unilateral inguinal bubo associated with lesions of scabies on the glans and shaft of the penis.



**Fig. 58.2:** Inguinal bubo associated with secondary pyogenic infection in primary syphilitic chancre. All such cases should be managed with using genital ulcer algorithm.

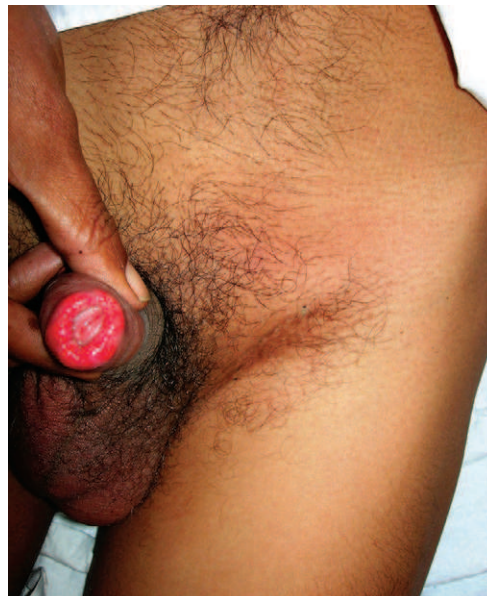


**Fig. 58.3:** Unilateral, fluctuant inguinal swelling due to chancroidal bubo.

and 58.4). LGV associated buboes are usually unilateral, but may be bilateral in up to one-third of cases (Fig. 58.5).<sup>19</sup> The femoral lymph nodes are involved in approximately 20% of patients. A recent case series from United Kingdom reported unilateral or bilateral inguinal lymphadenopathy in 12 out of 13 MSM patients presented with LGV. In this series only 4 patients had concurrent genital ulcers and 1 patient had only genital ulcer without lymphadenopathy.<sup>11</sup>

Both chancroid and LGV associated inguinal buboes may be associated with constitutional symptoms including fever in about 27% of patients.<sup>3</sup> The inguinal swelling predominantly comprises of an enlarged lymph node; however, subcutaneous edema and abscess may also contribute to it.

As bubo enlarges, the pain increases and patient walks with a limp, bent at the waist in an attempt to limit the pain.<sup>20</sup> The pain sometimes is so severe that the patient may report to emergency department where the syndrome may be mistaken for an incarcerated inguinal hernia.<sup>15,21</sup> The bubo becomes fluctuant (Figs. 58.3 and 58.4) in about 1–2 weeks and, if



**Fig. 58.4:** Multiple ulcers of chancroid with unilateral inguinal bubo.



**Fig. 58.5:** Bilateral inguinal buboes of lymphogranuloma venereum. Note impending rupture. *Courtesy: Kamal Aggarwal, Sanjeev Gupta, and Vijay K Jain, Rohtak, India.*

not treated, aspirated, or drained, it ruptures on the surface to form a sinus or non-healing ulcer (Fig. 58.6). Concomitant genital ulcer is seen more frequently in patients with chancroid. Overall, genital ulcers are seen in about 40% of all patients who present with inguinal buboes. All such patients should be managed as per the guidelines for the management of genital ulcers.<sup>2</sup>

### Laboratory Investigations

A raised peripheral leukocyte count ( $>10,000/\mu\text{L}$ ) can be present. In all patients, pus should be aspirated for a laboratory workup. If buboes are not fluctuant, then a saline aspirate may provide the desired material. A Gram stain of aspirated pus may reveal *H. ducreyi*; however, it is not a sensitive method. Culture of the





**Fig. 58.6:** Ruptured inguinal bubo due to chancroid in a woman.

aspirated pus may grow *H. ducreyi* in patients with chancroid. However, the colonies are sparse and scattered even if a large amount of pus is inoculated.<sup>3</sup> The aspirated pus should be tested for *C. trachomatis* by immunofluorescence with a monoclonal antibody based assay. Electron microscopy may reveal elementary and reticulate bodies. Culture in McCoy cells may grow *C. trachomatis*, LGV strains.<sup>22</sup> Polymerase chain reaction remains the most sensitive method,<sup>22</sup> although not available at most of the centers where the syndrome is endemic. An ulcer workup (as described in Chapter 53) is recommended if a concomitant genital ulcer is present.

## Syndromic Management

The laboratory tests described above are mostly not available where the syndrome of inguinal buboes is most prevalent. Therefore, the World Health Organization (WHO) has recommended that all patients with inguinal and/or femoral buboes should receive treatment for chancroid and LGV, without laboratory confirmation of the diagnosis. The WHO algorithm for management of the syndrome of inguinal and/or femoral bubo(es) is shown in Fig. 58.7.

In most Asian countries, *H. ducreyi* is resistant to tetracyclines<sup>23</sup>; therefore, all patients with inguinal bubo should receive the following regime<sup>2</sup>: Ciprofloxacin, 500 mg orally, twice daily for 3 days and Doxycycline, 100 mg orally twice daily for 14 days or Erythromycin, 500 mg orally four times daily for 14 days. Some cases may require treatment longer than 14 days. Several isolates of *H. ducreyi* with intermediate resistance to either ciprofloxacin or erythromycin have been reported worldwide.<sup>24</sup> Azithromycin (1g orally) and ceftriaxone (250 mg intramuscular) offer the advantage of single-dose therapy for chancroid.

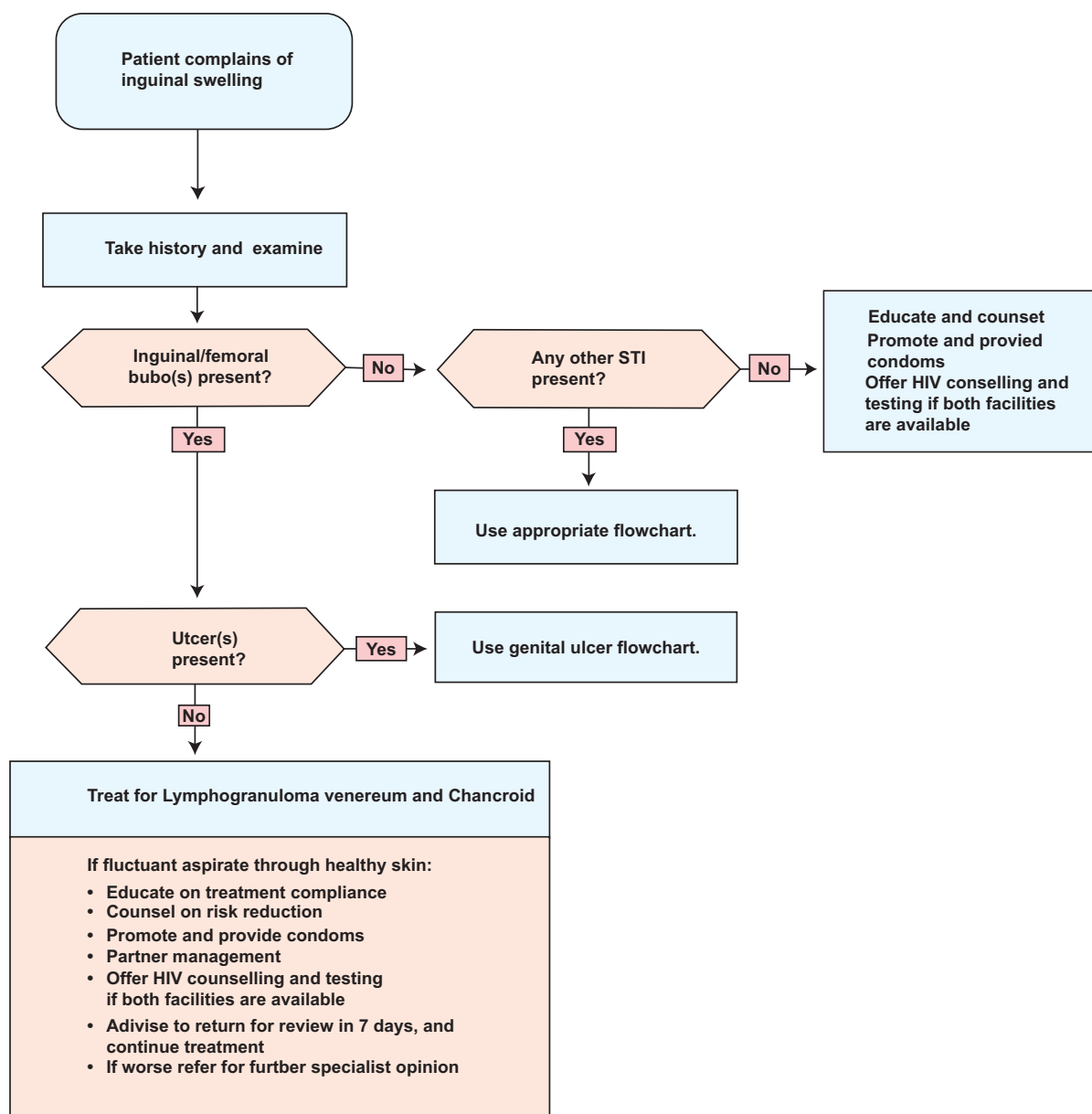
After initiation of therapy, patients usually improve symptomatically within 3 days and objectively within 7 days after therapy.<sup>24</sup> If no clinical improvement is evident at 1 week, the clinician must reconsider the diagnosis or rule out any coinfection with another STD or noncompliance and lastly resistant *H. ducreyi* strain<sup>24</sup> and the patient should be referred to a higher center for further management. Complete resolution of fluctuant buboes is slow.

The safety of azithromycin for pregnant and lactating women has not been established. Ciprofloxacin and doxycycline are contraindicated for pregnant and lactating women, children, and adolescents. So in such situations, erythromycin alone or in combination with ceftriaxone regimens should be used to treat inguinal bubo.

In patients coinfecting with HIV, there may be slower rate of healing or treatment failures. Recommended regimen is erythromycin base 500 mg orally four times a day for 21 days with or without ceftriaxone 250 mg intramuscular single dose. However, treatment failures have been frequently reported in HIV seropositive patients with chancroid from Africa for azithromycin,<sup>25</sup> ceftriaxone,<sup>26</sup> single-dose fleroxacin,<sup>27</sup> low-dose erythromycin or ciprofloxacin.<sup>28</sup> Such cases should be monitored closely.

## To Incise or not to Incise?

It is recommended that all fluctuant buboes should be aspirated with a 19 number needle through healthy skin to avoid rupture, which may result in sinus formation and delay in healing.<sup>2,17</sup> For this reason, most authors agree that incision and drainage or excision of nodes should be avoided.<sup>2</sup> However, in a study from the United States, Ernst et al.<sup>29</sup> compared incision and drainage and aspiration in fluctuant buboes of chancroid and concluded that the former may be preferable, as traditional needle aspiration requires frequent reaspirations. None of their patients developed discharging sinuses or nonhealing ulcers after incision and drainage. On the other hand, Lewis<sup>18</sup> opined that incision and drainage cannot be recommended in the tropics (where the “syndrome” is more prevalent) as it may be associated with increased postoperative morbidity.



**Fig. 58.7:** WHO algorithm for the management of inguinal buboes. *Courtesy:* WHO guidelines for the management of sexually transmitted infections. WHO/HIV/2003.09.

### Summary

- The syndrome of inguinal and femoral buboes is defined as the localized enlargement of the lymph nodes in the groin area that are painful, and may or may not be fluctuant.
- The most common causes of inguinal and/or femoral buboes are infection with *Haemophilus ducreyi*, the causative organism of chancroid, and *Chlamydia trachomatis*, L1-L3 strains, which cause lymphogranuloma venereum.
- Both chancroid and LGV are rare diseases even in tropical and subtropical regions; however, there has been a resurgence of LGV in Western Europe, United States and Australia in HIV positive MSM population, although the majority of them does not present with the classical inguinal syndrome. On the other hand it is common to see

inguinal suppuration as a complication of several other diseases, such as pyogenic infection of the leg, cat-scratch disease, tuberculosis, plague, guinea worm infestation and secondary pyogenic infections of genital ulcers due to other STD pathogens.

- Syndromic management of patients with inguinal bubo comprises of Ciprofloxacin, 500 mg orally, twice daily for 3 days and Doxycycline, 100 mg orally twice daily for 14 days, or Erythromycin, 500 mg orally four times daily for 14 days. In regions where Quinolone-resistant strains of *H. ducreyi* are reported, Azithromycin, 1g orally or Ceftriaxone 250 mg intramuscular are good single-dose alternatives.
- If patient has concomitant genital ulcer, they should be managed as per the guidelines for the management of genital ulcers.

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# section **X**

## **GENITAL DERMATOLOGY AND GENITAL PAIN SYNDROME** — *Mikhail Gomberg*

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## Introduction

Balanitis is an acute or chronic inflammation of the glans penis. Posthitis refers to an inflammation of the mucosal surface of the prepuce. The term balanoposthitis thus refers to an inflammation of the glans and penile mucosa. Balanitis is a common condition in male patients attending sexually transmitted diseases (STDs)/genitourinary medicine (GUM) clinics. There is scarcity of data on epidemiology of balanitis. The frequency of balanitis is reported to be 10.7% in Portugal and 11% in UK among men attending STD/GUM clinics with little information from other parts of world.<sup>1,2</sup> It can be a transient, recurrent, or persistent problem. Nevertheless, despite its frequency, this condition often receives scant attention.

Balanitis is more common among uncircumcised men, possibly as a result of poorer hygiene and aeration or because of irritation by smegma. Underlying medical conditions like diabetes mellitus can also predispose to balanitis, which may be more severe. Pre-malignant lesions of the balanopreputial area, although not frequent, represent a difficult diagnosis and therapeutic challenge.

The disease starts as inflammation with or without break in the continuity of the surface of glans or prepuce. This is followed by edema of the prepuce, phimosis, thin whitish or thick malodorous subpreputial discharge (minimal to copious) accompanied by pain, pruritus, and occasionally burning during micturition. Balanitis covers a variety of unrelated conditions with similar clinical presentation. It results from infective, irritative, allergic, traumatic, and inflammatory causes and pre-malignant lesions have also been identified (Table 59.1).<sup>3,4</sup> *Candida* species are considered to be the commonest cause of infective balanitis, most being sexually acquired.<sup>3-6</sup> The manifestations of balanoposthitis, irrespective of etiology, are much more severe in the presence of HIV infection, particularly in the advanced stages.<sup>7</sup> In this chapter, only the common and important conditions causing balanitis/balanoposthitis have been discussed.

## Balanitis in Children

Balanoposthitis in children is a rare entity. If present, it is usually seen in the age between 2 and 5 years and is primarily due to group

A  $\beta$ -hemolytic streptococci, where the mode of transmission appears to be autoinoculation from other sites.<sup>3</sup> It is often caused by mixed infection, which includes *Escherichia coli*, *Pseudomonas*, *Klebsiella spp.*, *Serratia spp.*, and *Streptococcus spp.* Such children present with an erythematous moist balanoposthitis secondary to a non-retractile prepuce.

## Balanitis/Balanoposthitis in Adults

### ETIOLOGY

The causes can be broadly classified under two groups—infections and dermatological diseases (Table 59.1).

### Infections

There are a wide variety of causes for balanitis, but infection is

**Table 59.1:** Etiology of Balanitis/Balanoposthitis

#### Infections

**Mycotic:** *Candida*, Dermatophytes, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Cryptococcus neoformans*, *Penicillium marneffei*

- **Bacterial:** *Streptococci*, *Staphylococcus aureus*, *Bacteroides spp.* and other Anaerobic bacteria, *Mycobacterium tuberculosis*, *Treponema pallidum*, *Haemophilus ducreyi*, *Mycoplasma*, *Neisseria gonorrhoeae*, *Gardnerella vaginalis*
- **Viral:** *Herpes simplex virus*, *Human papillomavirus*, *Herpes zoster virus*
- **Protozoan:** *Trichomonas vaginalis*, *Entamoeba histolytica*, *Leishmania*
- **Parasitic:** Scabies (*Sarcoptes scabiei* var *humanus*), cutaneous larva migrans (*Ancylostoma braziliense* etc.)

#### Dermatological diseases

- Allergic & irritants contact dermatitis
- Dermatoses (see Table 59.2)
- Premalignant conditions—Bowen disease, erythroplasia of Queyrat
- Malignancy—squamous cell carcinoma, basal cell carcinoma, metastasis.

#### Adverse drug reactions

Sulfonamides, analgesics, anticonvulsants, chemotherapeutic agents, foscarnet, warfarin

#### Miscellaneous

Trauma, viz. zip fastening, due to beads, piercing of the frenulum, etc.

the most common reported etiology. In a study from Sweden consisting of 100 patients with balanoposthitis, there was a significantly higher frequency of positive cultures than in the control group (59% and 35%, respectively;  $p < 0.05$ ). *Staphylococcus aureus* was found in 19%, group B streptococci in 9%, *Candida albicans* in 18%, and *Malassezia* in 23% of patients. In the control group, *S. aureus* was not found at all, whereas *C. albicans* was found in 7.7%, and *Malassezia* in 23% of men.<sup>8</sup>

Among 219 men with balanitis attending the STD Clinic of Hospital de S. João, a university hospital in Porto, Portugal, between 1995 and 2004, 118 (53.9%) had clinically been assumed to suffer from infective balanitis. In 75 (63.6%) patients, the diagnosis was confirmed by culture studies. *C. albicans* was isolated from 24 (32%) patients. *Staphylococcus spp.* and groups B and D streptococci were the most frequently isolated bacteria.<sup>2</sup>

### Mycotic Infections

**Candidal Balanoposthitis** This is considered to be the most common cause and is usually due to infection with *C. albicans*. First described by Engman in 1920, candidal balanoposthitis is a well-recognized condition responsible for up to 35% of all cases of infectious balanitis.<sup>2,5</sup> There is little information about candida colonization and infection in men.<sup>9</sup> According to several studies, less than 20% of unselected males may carry yeasts on the penis.<sup>10,11</sup> Reported predisposing factors for male genital candidosis include diabetes mellitus, immunosuppression, uncircumcised state, having a sexual partner with vulvovaginal candidiasis or a recent use of antibiotics.<sup>2,3,12,13</sup>

In a study of 478 men attending a STD clinic in Portugal, the prevalence of candida colonization was 26.2% and of candidal balanitis was 18%. At age above 40 years, diabetes mellitus and more than 10 candida colonies recovered by culture were risk factors for candida balanitis. Surprisingly, no significant association was noted between uncircumcised men and candida infection in this study.<sup>14</sup>

Although carriage of yeasts on the penis is not uncommon, only a few get the symptomatic disease. Candida balanitis is more prevalent in men having sexual partners with vulvovaginal candidiasis.<sup>15</sup> It is generally acquired sexually and is often self-limiting. The clinical features of candida balanitis include mild-glazed erythema and papules with or without satellite pustules on the glans penis. These break to leave behind superficial erosions with a collarette of whitish scales with moist and curdy accumulation under the prepuce. These infections can spread to involve the scrotum and the groins. In circumcised patients, there may be a red glazed appearance of the glans with a slightly scaly edge. Usually, patients complain of local burning and pruritus; however, this clinical aspect is often non-specific.<sup>2</sup> In men with diabetes mellitus or in immunocompromised hosts, an acute fulminating edematous or ulcerative variant may occur.<sup>16</sup> Diabetic candidal balanitis occurs not infrequently in older males, often with a fissured and slightly indurated prepuce that is difficult to retract. In a study of infective balanitis, 76.9% of patients with microbiologically

confirmed candida balanitis had diabetes mellitus.<sup>2</sup> There are often symptoms of vague ill health rather than classical symptoms of the onset of diabetes mellitus in younger persons.<sup>17</sup> Occasionally, a patient develops a hypersensitivity reaction to yeast infection in the partner. This presents with burning and redness, which occurs a few hours after intercourse, but is actually without infection on microscopy and/or culture.<sup>16,18</sup>

In practice, candida balanitis is often a clinical diagnosis without systematic laboratory confirmation; however, some investigators have stressed the relevance of the isolation of yeasts for the definitive proof of a fungal infection.<sup>14</sup> On microscopy, pseudohyphae can be easily identified in KOH, saline, or Gram stained preparation. It is known that the sampling method for culture has a strong influence on the percentage of isolates. The quantity of material collected is often small and it certainly contributes to the incidence of negative cultures. In clinically suspected cases of candidal balanitis, culture negativity of up to 36% has been reported.<sup>2</sup> Adhesive tape method has been proven to be more accurate than swabbing. Improved diagnostic procedures, with higher sensitivity and specificity, are mandatory in order to rule out an over-diagnosis of candida balanitis. Serum glucose levels and urine analysis to exclude diabetes mellitus are usually recommended in men with candida balanitis.<sup>19</sup> Candidal balanitis is often commonly confused with irritant balanitis, circinate balanitis, contact allergy, or plasma cell balanitis of Zoon.

**Treatment:** Diagnosis based solely on clinical grounds is often inadequate. Some patients are often assumed to suffer from candida balanitis without laboratory confirmation. Underlying disorders causing the infection should be addressed. Subpreputial normal saline washes twice daily are an essential prerequisite. Once the condition has subsided, daily washing under the foreskin is to be maintained as a regular habit. It is important to emphasise that both partners should be treated at the same time. There could be recurrent episodes of infection.

Treatment options usually involve topical or oral azole agents. Clotrimazole, miconazole, and econazole are the topical antifungal agents usually recommended. Topical azoles applied twice daily have been shown to have a cure rate of more than 90%. Oral treatment with fluconazole (150 mg as a single dose) is recommended when symptoms are severe, in recalcitrant cases, or with concomitant diabetes. A single dose of fluconazole, 150 mg orally, has been shown to be effective in up to 100% of the cases.<sup>20</sup> In case of presence of candidal hypersensitivity, a combination of a mild topical corticosteroid and an antifungal may be more effective.

**Dermatophytes** *Trichophyton rubrum* and *T. mentagrophytes* are rare causes of balanoposthitis. Six cases have been reported from Japan.<sup>21</sup> In a report of nine cases from Italy, the lesions, situated on the penis, glans, and scrotum, were preceded by dermatophytosis in other sites (groins: five cases; feet: two cases; toenails: 2 cases; hands in one; and beard in another). Mycological examination consisting of direct microscopy and culture led to isolation of *Trichophyton rubrum* in five cases,

*Epidermophyton floccosum* in two, and *T. mentagrophytes* var. *interdigitalis* in the others. Clinical diagnosis is not always easy. In three cases the lesions had been misdiagnosed as eczema.<sup>22</sup> A 27-year-old Japanese male student with tinea of the glans penis having lesions as crop of papules has been described.<sup>23</sup> Topical antifungals normally suffice, oral antifungals like griseofulvin or fluconazole may be more effective.

**Pityriasis Versicolor** Glans penis involvement is generally reported in association with extensive skin involvement. The causative organism is *Malassezia furfur* and diagnosis can be confirmed on KOH examination or culture. Despite the common occurrence of pityriasis versicolor of the skin, involvement of glans penis is rarely noted with only few cases in literature indicating that this might be missed, undiagnosed, or diagnosed as other condition. They present clinically as discrete, circinate, finely scaly, hypopigmented areas on the glans, which fluoresce yellow under Wood's light. The lesions can be treated with topical azoles.<sup>24</sup>

**Deep Fungal Infections** Disseminated *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Cryptococcus neoformans*, and *Penicillium marneffei* can cause balanitis. *Histoplasma* balanitis manifests as punched out ulcers, which are non-tender and have an indurated margin. *Cryptococcus neoformans* produces a necrotizing balanitis in HIV positive individuals. *P. marneffei* can cause ulcerative balanitis in HIV positive men. The infections respond to surgical debridement, intravenous amphotericin B and, oral ketoconazole.<sup>25</sup>

### Bacterial Infections

Bacteria represent the second most common cause of infectious balanitis, *Streptococcus* spp. being most frequently incriminated. The pathogenic nature of some bacterial isolates from glans penis remains controversial. Their presence does not necessarily mean that they are the cause of balanitis, as such organisms are common members of the indigenous mucosal microbial population.<sup>16</sup> Some authors have reported that bacteria, such as *Staphylococcus epidermidis*, *Klebsiella*, *Enterococcus*, and *Escherichia coli* may cause mild balanoposthitis.<sup>26</sup>

**Syphilitic Balanitis of Follman** It is rare. It appears in the later stages of primary syphilis or early in secondary syphilis (Figs. 59.1 and 59.2). It presents as multiple circinate lesions, which erode to cause irregular ulcers, or as a swollen glans covered with partially coalescent white flat papules and plaques.<sup>3</sup> Rarely, this form of balanitis may present with multilocular pustules.<sup>16</sup> Spirochaetes can be demonstrated from the lesions through dark-field examination. It is possible that cases of Syphilitic balanitis of Follman are in reality much more frequent than is generally recognized; when treponemes are found in a primary chancre in the region of the glans or prepuce, we do not normally look further for them in the frequently accompanying inflamed glans penis.<sup>27</sup> Patient should be managed as per CDC/WHO recommendations for the stage of syphilis. Benzathine penicillin 2.4 million units as a single intramuscular injection (half in each buttock, after a test dose) is effective.<sup>28</sup>



Fig. 59.1: Primary syphilis ulcer on glans penis.



Fig. 59.2: Secondary syphilis rash involving penis.

**Chancroid** The glans penis and prepuce are nearly always affected in the disease caused by *Haemophilus ducreyi*. The typical clinical presentation is painful shallow ulcers with ragged and undermined edge, granulomatous base, and purulent exudate. Complications include phimosis in men, phagedenic ulceration due to secondary bacterial infection and typically a posthitis is found with preputial fissuring. Treatment is with adequate doses of erythromycin, ceftriaxone, azithromycin, or ciprofloxacin.<sup>28,29</sup>

**Chlamydial Balanitis** *Chlamydia trachomatis*, specifically D to K serotypes, is responsible for a large number of genital infections like non-specific urethritis, epididymitis and epididymo-orchitis, but little is known about the epidemiology of local complications in men. Balanitis arising in a patient with non-gonococcal urethritis (NGU) or proctitis should raise suspicion of this condition.<sup>16</sup> Tetracyclines or other drugs recommended for chlamydial infection should be given in adequate doses.<sup>25</sup>

**Mycoplasma Balanitis** It is observed in about 10% of patients with NGU caused by mycoplasmas. Clinically, it presents as simple erythema or circinate lesions, which have a tendency to hemorrhage. Mycoplasmal balanitis may also occur with no evidence of concurrent dysuria.<sup>16</sup> Detection of *M. genitalium* in men with acute NGU is associated significantly with balanitis and/or posthitis. The association is biologically plausible and may have a role in HIV-1 transmission and susceptibility.<sup>30</sup> It should be treated with systemic tetracyclines.



**Gonococcal Balanoposthitis** Infection of penile skin and subpreputial mucosa by *Neisseria gonorrhoeae* is less common. Gonococcal balanoposthitis can be a primary manifestation of this infection. It presents as tender ulcers, pustules, or furuncles on the prepuce or shaft of the penis. Abscesses of the prepuce and progressive ulceration of the glans with lymphadenopathy may also be seen. The incubation period is 2 to 10 days and trauma is not a prerequisite. These infections may occur in the absence of urethral symptoms although urethral swabs obtained from 4 of 6 patients, in a study, were positive for *N. gonorrhoeae*.<sup>16</sup> Recurrent gonococcal balanoposthitis may result in secondary hypopigmentation of the glans. The infection is confirmed by Gram stain of pus demonstrating intracellular gram-negative diplococci, and also by culture. Recommended treatment includes a single dose of ceftriaxone, cefixime, or ciprofloxacin. Recently, quinolone resistant strains have become prevalent in many Asian countries. Simultaneous treatment with doxycycline or azithromycin for *C. trachomatis* is also advocated.<sup>28</sup>

**Gardnerella Vaginalis** It has been isolated in 31% of the patients with non-candidal balanoposthitis and up to 75% of these cases have a concomitant infection with anaerobic pathogens (*Bacteroides* spp.).<sup>31</sup> It is likely to be sexually acquired, as evidenced by high isolation rates from urethra or urine in partners of women with *Gardnerella vaginalis* vaginitis. The symptoms of pure *Gardnerella* infection are milder than those in combination with anaerobic infection. The clinical features include irritation of the prepuce and the glans penis, macular erythema, and a subpreputial discharge with fishy odor. Treatment is with metronidazole along with good local hygiene.

**Group B Streptococci** These are usually carried asymptotically in the adult genital tract but may sometimes be associated with balanitis. Rate of carriage on the glans in heterosexuals and homosexuals varies between 16.6% and 39.3%, respectively,<sup>16</sup> although no balanitis has been reported from the latter group. The role of sexual transmission though was unclear earlier,<sup>32</sup> it is now considered to be sexually transmitted.<sup>33</sup> Clinically, streptococcal balanitis presents as a non-specific erythema, with or without discharge. More rarely, if abrasions are present, streptococci may invade deeper tissue to produce penile cellulitis.<sup>34</sup> Group A  $\beta$ -hemolytic streptococci have also been reported as a cause of balanitis, more commonly in uncircumcised children. They present with erythematous moist balanitis, where the mode of transmission is autoinoculation.<sup>35</sup> Following fellatio, pyoderma caused by group A  $\beta$ -hemolytic streptococci has been reported. In a study of 189 adult patients with balanoposthitis, *Streptococcus pyogenes* was isolated in 47 cases with route of infection considered to be predominantly sexual.<sup>36</sup> Penicillins and cephalosporins are effective in the treatment.

**Staphylococcus Aureus** This organism is an infrequent cause of balanitis. Although carriage is not associated with symptoms, toxic shock syndrome occurring after a *Staphylococcus aureus* balanitis has been documented in a 5-year-old boy.<sup>37</sup>

**Anaerobic Bacterial Infection** Erosive and gangrenous balanitis resulting from a symbiotic infection of anaerobes and non-treponemal spirochaetes account for 8–30% of all cases of ulcerative balanoposthitis.<sup>38,39</sup> *Bacteroides* spp. are the most common isolates from these mixed infections. Cree et al.<sup>40</sup> proposed the term anaerobic erosive balanitis for this condition.

The microorganisms that cause anaerobic balanitis may be transmitted from mouth by fingers contaminated with saliva or more commonly orogenital contact.

All reports of anaerobic erosive balanitis have been in uncircumcised males. Predisposing factors include relative phimosis and poor local hygiene. Patients initially have extensive tender erosions of the glans accompanied by foul-smelling discharge. Edema of the prepuce causing phimosis is not uncommon. Diagnosis is confirmed by gram staining, dark-field examination, and culture. Transmission is thought to occur most commonly by orogenital contact. The response to treatment with metronidazole is rapid, whereas neglected cases may progress to phagedenic complications.

Necrotizing fasciitis of the male genitalia originally described by Fournier, is rare. Paraphimosis, penile erosions, local trauma, circumcision, and periurethral abscesses have been associated with necrotizing fasciitis of the penis. Clinically, the infection begins as an area of cellulitis which may progress to a blue-brown ecchymotic discoloration.<sup>16</sup> The lesion is extremely painful. Mixed population of gram negative bacilli and anaerobes, especially *Bacteriodes* spp. are isolated most commonly. Diabetes mellitus seems to be a predisposing factor. Broad-spectrum antibiotics are required. Sometimes surgical debridement may be necessary.

### Viral Infections

**Herpes Simplex Virus** Primary genital herpes is classically characterized by multiple grouped vesicles in bilateral distribution, moderate-to-severe local pain and dysuria, with tender inguinal lymphadenopathy, and systemic symptoms. Rarely, primary herpes can cause a necrotizing balanitis presenting with a necrotic black eschar on the glans accompanied by vesicles elsewhere. This may be associated with headache, dysuria, fever, and inguinal pain.<sup>41–43</sup>

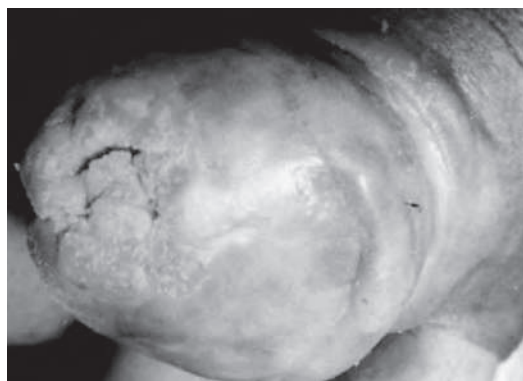
Recurrent and persistent ulcerative herpes simplex virus lesions are among the most common infections amongst the patients with HIV/AIDS. Extremely painful, persistent, large, and necrotizing ulcerated areas involving the prepuce, glans, shaft of the penis, and pubic region in males can occur in HIV seropositive individuals with advanced disease.

Treatment is with acyclovir, which requires a prolonged course in the HIV infected.

**Human Papillomavirus** Majority of the anogenital warts are caused by human papillomavirus (HPV) infection. It is one of the most common sexually transmitted disease with a rising incidence. HPV produces the classical warty lesions on any part of the male genitalia, commonly known as condyloma acuminata. Although very uncommon, a verrucous carcinoma that is locally aggressive but rarely metastatic, the Buschke–Löwenstein tumor



**Fig. 59.3:** Buschke–Löwenstein tumor (giant genital wart).



**Fig. 59.4:** HPV balanitis (pseudoeplitheliomatous keratotic and micaceous balanitis).

(Fig. 59.3) may be seen. Rarely a picture with hypertrophic and hyperkeratotic plaque lesions (PEKB) on the glans may occur (Fig. 59.4). HPV may be associated with a chronic balanitis presenting as patchy maculopapules or erythematous macules on the inner aspect of prepuce and glans (Fig. 59.4).<sup>44</sup> This becomes acetowhite after application of 5% acetic acid. It is a non-specific test, as other inflammatory lesions may also provoke similar changes on acetic acid application. In one study up to 44% of men with HPV balanoposthitis had macular lesions. Symptoms included redness, itching, burning, tenderness, and fissuring of the glans.<sup>45</sup> Lowhagen et al.<sup>46</sup> demonstrated high-risk HPV types (6, 18, 31, and 33) in 56% macular lesions. Uncircumcised men are more susceptible to this condition.<sup>16</sup> In atypical cases of balanoposthitis, HPV etiology should also be considered. Treatment is with podophyllotoxin, imiquimod or topical 5-fluorouracil, all of which have been found to be effective. Bowenoid papulosis appear as 2-to-3 mm papules, often multiple on external genitalia including glans penis (Fig. 59.5). Histologically there is cellular atypia resembling Bowen disease or squamous cell carcinoma *in situ*. These lesions are usually infected with HPV-16, which suggests that bowenoid papulosis may represent a precursor of penile cancer.



**Fig. 59.5:** Bowenoid papulosis.

### Protozoal Infections

**Trichomonas Vaginalis** Although *T. vaginalis* infection is regarded primarily as a disease of women, it also occurs in men. About 15–50% men with trichomonal infection remain asymptomatic carriers. In symptomatic men, common complaints include scanty, clear to mucopurulent discharge, dysuria, and mild pruritus or burning sensation immediately after sexual intercourse. Other symptoms include urethral irritation and frequency. Rarely the patient may complain of copious purulent urethral discharge, or complications such as prostatitis and epididymitis. *T. vaginalis* infection may present as an erosive balanitis, which may lead to phimosis.<sup>16</sup> A long prepuce has been noted as a predisposing factor. A wet mount from the subpreputial sac may demonstrate the organism. The condition responds well to metronidazole.<sup>47</sup>

**Amoebic Balanitis** First reported by Straub in 1924, it is caused by a protozoan *Entamoeba histolytica*. Two modes of transmission are recognized; autoinoculation from amoebic dysentery and vaginal or anal intercourse with an infected person. This severe form of balanitis is marked by edema with phimosis, pain, dysuria, and ulceration of the glans penis. Clinically, the lesions may suggest an ulcerative carcinoma, but the major distinguishing feature is the presence of pain. The diagnosis in men was made by biopsy, culture, smear, or wet preparation. Genital amoebiasis lesions generally respond swiftly to a standard course of metronidazole treatment (800 mg three times daily for 5 days). Circumcision may be required in some cases.<sup>7,48</sup>

### Parasitic Infection

**Scabies** It is an infestation with a mite, *Sarcoptes scabiei var hominis*. Primary lesions in scabies are burrows, papules, vesicles, and small nodules. Burrows are the pathognomonic lesions and are 5–15 mm long linear eruptions most frequently found in the web spaces of the fingers, sides of the hands, and flexor surfaces of the wrist. More common than the burrows are the erythematous papules, which are more extensively distributed. The chief clinical symptom is pruritus, which is usually worse at night. Sometimes scabietic lesions are seen predominantly over the



**Fig. 59.6:** Scabies with genital involvement.

genitalia (Fig. 59.6) in adult males which may indicate a sexual transmission. They are raised, slightly elongated, nodular lesions with the burrow tracks each seen as a thin, black, and irregular line. Mechanical scratching by the patients removes the roof of the burrow leaving a shallow longitudinal ulcer. The lesions are commonly seen on the preputial skin, shaft of penis, scrotum, and glans penis. The preferred treatment for scabies is permethrin 5% cream applied from neck to the feet, with particular attention given to the perianal and genital areas, and to the free nail edge and folds; the cream is rinsed off after 8–14 hours. All household members of the scabietic patient, and any sexual partners, should be treated concomitantly.<sup>16</sup>

## Dermatological Diseases

### Allergic and Irritant Contact Dermatitis

Allergic contact dermatitis of the genital area may result from condoms, lubricants, feminine hygiene deodorant spray, cauterizing agents, habit of applying strong antiseptics to avoid getting STDs after sexual exposure, and use of spermicides. Involvement of the adjacent area may give the clue to the underlying etiology. More often, contact dermatitis is irritant, resulting from persistent moisture and maceration. Clinically, genital allergic contact dermatitis is characterized by erythema, edema, and exudation (Fig. 59.7).<sup>16</sup> Acute contact dermatitis of the penis is



**Fig. 59.7:** Allergic contact dermatitis leading to paraphimosis.

usually associated with marked edema because the skin covering the genitalia is thin and elastic. Men using latex contraceptive products may present with edematous, weeping eruption of acute contact dermatitis.<sup>49</sup> Rarely, immediate hypersensitivity reaction may be life-threatening.

Irritant contact dermatitis results from non-immunological physical or chemical damage to the skin. The eruption primarily occurs in the area of contact with irritants, and may develop from the use of certain soaps, detergents, or topical medications. In the acute phase, the lesions are erythematous, oozy, and crusted, whereas with recurrent or prolonged exposure to irritants, the skin becomes lichenified and hyperkeratotic. There is a wide spectrum of clinical manifestations varying from mild balanitis to edema of the whole penis extending to the groins.

Mild cases can be treated with low potency corticosteroid creams. Severe cases of allergic contact dermatitis may require treatment with systemic corticosteroids. The identification of the contact allergen depends on history and usually requires “patch” testing. This procedure is especially indicated for cases in which inflammation persists despite avoiding the suspected allergens and after appropriate topical therapy. Management will depend on the severity of the reaction and avoidance of the precipitant is required.<sup>50</sup> Topical treatment with emollients/moisturizers in addition to specific therapy is helpful in majority of these patients.

### Dermatoses Causing Balanitis

Many dermatological conditions may also have a predilection for the male genitalia (Table 59.2). Psoriasis, lichen planus, and seborrheic dermatitis are common and evidence of involvement at other sites should be sought. In many cases, male genital

**Table 59.2:** Dermatoses Causing Balanitis/Balanoposthitis

- Psoriasis
- Lichen planus/nitidus
- Fixed drug eruptions
- Erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis
- Seborrheic dermatitis
- Pityriasis rosea
- Crohn disease
- Ulcerative colitis
- Autoimmune blistering disorders—Pemphigus, bullous pemphigoid, cicatricial pemphigoid, linear IgA disease, epidermolysis bullosa acquisita
- Lichen sclerosis (balanitis xerotica obliterans)
- Plasma cell balanitis (Zoon balanitis)
- Necrobiosis lipoidica
- Hypereosinophilic syndrome
- Reiter syndrome (balanitis circinata)
- Xanthomatosis
- Histiocytosis
- Sarcoidosis
- Porokeratosis
- Leprosy
- Aphthous ulcer (Behcet disease)
- Pyoderma gangrenosum





**Fig. 59.8:** Psoriasis involving glans penis.



**Fig. 59.9:** Lichen planus involving glans penis.

involvement with psoriasis is part of a more generalized cutaneous disorder. The typical psoriatic scale is usually not apparent because of moisture and maceration (Fig. 59.8). Lichen planus presents with violaceous flat-topped papules and frequently annular lesions on the glans and shaft of the penis (Fig. 59.9). Balanitis may occur both with Crohn disease and ulcerative colitis involving the perianal and genital areas. Dermatitis artefacta of the genitals has also been reported.

### Lichen Sclerosus

Lichen sclerosus (LS) of the male genitalia is a chronic inflammatory disorder presenting as a chronic, sclerosing atrophic process of the glans and foreskin, leading to meatal stenosis and acquired phimosis. Most authors consider LS of the penis synonymous with balanitis xerotica obliterans.<sup>51,52</sup> It can remain completely asymptomatic for some time however, the main symptoms are pain, irritation, disturbance of sexual function, and urinary symptoms including obstruction. The initial lesions of LS are white, polygonal, and flat-topped papules or plaques. The lesions progress to ivory colored atrophic and sclerotic white plaques. Rarely, this can present as a recurrent bullous balanitis, with the development of painful blisters and ulceration that may be precipitated by local trauma. The clinical appearance is of porcelain white plaques on the glans, often with involvement of the prepuce, which becomes thickened, and non-retractile and fissures develop on attempted retraction. In active disease,

hemorrhagic vesicles may be seen. The changes affect squamous skin, leaving atrophic areas that cause cicatricial shrinkage leading to urethral stenosis and phimosis.<sup>50–52</sup>

The condition may affect any age group, but is most common in middle-aged uncircumcised men. The incidence of genital LS in young boys with phimosis has been estimated to be about 15%, and circumcision specimens from children with phimosis often show the characteristic histological changes.<sup>53</sup> In a prospective study of 43 men with narrowing of the prepuce referred for circumcision, LS was present in 32%. Of these only 21% of the men had been clinically diagnosed as having LS.<sup>54</sup> Histology initially shows a thickened epidermis, followed by atrophy and follicular hyperkeratosis, basal cell degeneration, upper dermal edema, homogenization of collagen, and a chronic inflammatory infiltrate. The course is chronic and relapsing, and although it may sometimes arrest, but the areas of atrophy do not regress.

The association between LS and squamous cell carcinoma (SCC) is a well-known phenomenon in women, and it has been observed in 3–6% of patients with vulvar involvement. There are reports of men developing penile SCC in association with LS.<sup>50</sup> In a retrospective study of 86 uncircumcised patients with LS, five (6%) developed malignant changes.<sup>55</sup> Three patients had SCC, one had carcinoma *in situ* and one had verrucous carcinoma. The presence of HPV 16 was shown by PCR in four of the five cases. In a study of 20 patients with penile SCC, half had histological evidence of LS.<sup>56</sup> Periodic follow-up of patients with LS is advisable, including biopsy of any clinically suspicious lesion.

Biopsy is not essential in all cases and is indicated in atypical cases to differentiate from penile cancer. Early diagnosis and treatment of LS are very important in preventing the urological complications of the diseases such as urethral stricture. Treatment of LS depends on the anatomic location of the lesions and their extent and severity, together with the rapidity of progression of the disease process. Short courses of potent topical corticosteroids form the mainstay of treatment.<sup>51–53</sup> Topical pharmacotherapy is useful in the early stages to reduce the initial symptoms and slow down the progression, but is not effective in all cases and is not curative. Meatal stenosis, phimosis, scar adhesions, fissures, erosions of glans and prepuce, and involvement of the urethra are indications for surgical treatment.<sup>51,52</sup>

Recently topical calcineurin inhibitors (tacrolimus, pimecrolimus) have been found to be effective in patients not responding to corticosteroid treatment and as maintenance or combination therapy with topical corticosteroids.<sup>57,58</sup> However, concerns remain with regard to their malignant potential with long-term use. As LS is a potentially precancerous dermatosis, topical calcineurin inhibitors should be used with caution in this disorder.<sup>57</sup> In a placebo-controlled randomized trial, acitretin was found to be safe and effective for the management of severe, long-standing LS of the male genitalia.<sup>59</sup> Other therapies tried in LS are topical calcipotriol, photodynamic therapy, and laser ablation. Testosterone ointment has also been advocated.<sup>60</sup>

### Plasma Cell Balanitis (PCB)

PCB or balanitis circumspecta plasmacellularis is a benign, idiopathic condition first recognized by Zoon in 1952. PCB typically presents as a solitary, smooth, shiny, red-orange plaque on the glans and/or the prepuce of an uncircumcised, middle-aged to older man. The lesion often exhibits pinpoint purpuric cayenne pepper surface spotting with an area of yellow hue. Vegetative, erosive variants, and multiple lesions have been reported.<sup>16</sup> Lesions analogous to PCB have been reported on the vulva, nose, lips, oral cavity, epiglottis, and larynx. PCB tends to be chronic and is often present for months to years before the patient reports for consultation. Symptoms are minimal, but may include mild tenderness pruritus and subpreputial discharge.

Diagnosis is confirmed by the distinctive histological findings of epidermal atrophy with complete effacement of the rete ridges. Diamond shaped “lozenge keratinocytes” are common with uniform intercellular spaces termed “watery spongiosis.” A dense lichenoid subepidermal infiltrate composed largely of plasma cells is characteristic. Erythrocyte extravasation, hemosiderin deposition and epidermal ulceration are often noted.<sup>61</sup> All confirmed cases have involved uncircumcised men. The etiology and pathogenesis of PCB is speculative; heat, friction, poor hygiene, chronic infection with *Mycobacterium smegmatis*, trauma, response to an unknown exogenous agent, immediate hypersensitivity response to IgE class antibodies, and hypospadias have been implicated as predisposing factors. The treatment of choice for PCB is circumcision.<sup>62</sup>

Temporary relief is usually achieved by topical corticosteroids, with or without topical antibiotics or antifungals, but these are generally not curative. Resistant cases can be treated with the carbon dioxide laser or erbium-YAG laser ablation.<sup>63</sup> Recently, topical calcineurin inhibitors (tacrolimus, pimecrolimus) have been used as second-line treatment agents with limited success in patients with refractory lesions or in those not opting for circumcision.<sup>64–66</sup>

The distinction of this lesion from similar lesions is rather important, and a large group of disorders such as premalignant, infective, and other inflammatory penile diseases should be definitely taken into consideration in the differential diagnosis. It seems that circumcision might be the current “gold standard” for treatment of this disorder.<sup>67,68</sup>

### Circinate Balanitis

Balanitis circinata is a rather classic mucocutaneous manifestation of Reiter syndrome, a multisystem disease that is clinically characterized by the triad of nongonococcal urethritis, arthritis, and conjunctivitis. Balanitis circinata has been reported in 12–70% of men with Reiter disease. Circinate balanitis manifests as a well-demarcated, moist, erythematous plaque with a ragged or scalloped white border on the glans penis (Fig. 59.10). In circumcised patients, the lesions are dry and hyperkeratotic, and may appear as psoriasiform plaques.<sup>50</sup> It is characterized histologically by parakeratosis, acanthosis, and elongation of rete



Fig. 59.10: Circinate balanitis.

ridges. Dermal capillaries are enlarged and increased numbers are present together with a mononuclear cell infiltrate, and some evidence of extravasation. These changes are similar to those of pustular psoriasis. Circinate balanitis may occur with or without other features of Reiter syndrome. In one series, 9 of 17 patients had balanitis alone. The association with HLA B27 was observed in 15 of these patients.<sup>69</sup>

A complementary use of topical tacrolimus in 3 cases of circinate balanitis not responding satisfactorily to systemic antirheumatic drugs is reported.<sup>70</sup>

### Adverse Drug Reactions

Fixed drug eruptions have a predilection for the glans penis, and are commonly related to therapy with antibiotics, especially tetracyclines and sulfonamides. Other offending drugs include analgesics and anticonvulsants. Lesions are usually present as well-demarcated erythematous areas, which may be bullous and subsequently get ulcerated (Fig. 59.11).<sup>16</sup> This can occur on the first exposure to a drug. Repeated exposures will precipitate new lesions at the initial site (this helps to even confirm the diagnosis). Though the reactions usually occur with chemically related drugs, tetracycline induced eruptions may not recur on challenge with doxycycline. Most lesions fade spontaneously without treatment, but may leave an area of residual hyperpigmentation. Occasionally, treatment with topical, or rarely, systemic steroids may be required.<sup>71</sup> Identification and



Fig. 59.11: Fixed drug eruption.



avoidance of the offending drug are essential to avoid recurrences. Stevens–Johnson syndrome and toxic epidermal necrolysis are serious adverse drug reactions predominantly affecting mucous membranes including genital mucosa. Symptoms begin with burning sensations, target lesions, necrosis of mucous membrane of glans penis/prepuce leading to severely painful erosions covered by necrotic epithelium, and fibrin and/or hemorrhagic crusts. Scarring of mucosal sites is a frequent late complication leading to obliteration of the fornices and strictures. Stopping suspected drug at the earliest, halting the progression of disease, and supportive care are the cornerstones of treatment.

### Bullous Disorders

Mucosal involvement including that of genital mucosa is common in pemphigus. This autoimmune bullous disorder may cause erosions resembling balanitis. Pemphigus vulgaris can cause the clinical picture of balanitis xerotica obliterans and pemphigus vegetans, a rare variant, manifests as vegetating plaques. The lesions usually occur in intertriginous areas but may also affect the glans penis. Rarely, bullous pemphigoid, linear IgA disease, and mucous membrane pemphigoid may cause erosion and scarring simulating balanitis. Treatment depends upon severity of the disease which generally includes systemic immunosuppressives apart from topical corticosteroids.

### Erythroplasia of Queyrat

This is a manifestation of carcinoma *in situ*, which was described by Queyrat in 1911. It has a characteristic red, velvety appearance with sharp margins and a granular surface, usually occurring in uncircumcised men over 40 years of age. The lesions may be single or multiple, and if keratotic or indurated suggest the development of frank SCC. A definite diagnosis is made by a biopsy showing the typical histological picture of intraepidermal carcinoma *in situ*. Early invasion should be excluded by obtaining several biopsies. Transformation of erythroplasia into SCC has been reported to occur in 10–33% of cases.<sup>72</sup> There are various treatment options including 5-fluorouracil, cryotherapy, carbon dioxide laser, or surgical excision. Circumcision is recommended and close follow-up advised.<sup>68</sup>

### Miscellaneous

A wide range of infectious, neoplastic, and inflammatory dermatoses can affect the male genitalia. Several common diseases may involve the genital region only incidentally, while others present in this region with unusual features. In addition, there are some conditions that are entirely or predominantly confined to these regions.<sup>73,74</sup>

Papulonecrotic tuberculid present as chronic, recurrent, discrete, dusky red, inflammatory, papular eruptions leading to ulceration, crust formation and scarring of glans penis (Fig. 59.12). The lesions respond satisfactorily to antitubercular therapy. Biopsy and tuberculin testing should be carried out in all doubtful cases: a therapeutic test is usually decisive.<sup>75</sup>



**Fig. 59.12:** Papulonecrotic tuberculid.

Porokeratosis involving the genital area is uncommon and can occur as part of generalized involvement or as localized porokeratosis that is confined to the genital area. Lesion over glans penis is characterized by centrifugally spreading patches, which are surrounded by a ridge-like border with central atrophy. Treatment of localized genital porokeratosis includes cryotherapy, carbon dioxide laser, surgery, topical 5-fluorouracil, imiquimod, or topical diclofenac.<sup>76</sup>

Cutaneous leishmaniasis involving genitalia is rare. It is characterized by chronic localized ulceration developing at the site of inoculation. The diagnosis is confirmed by demonstrating the presence of *Leishmania* amastigotes in smear or biopsy material. Post-kala-azar dermal leishmaniasis present as papules and nodules over glans penis/prepuce in addition to involvement of other body sites. Treatment is usually either systemic or local pentavalent antimonial therapy depending on the species and clinical picture.

Patients with lepromatous disease and rarely tuberculoid leprosy occasionally develop skin lesions of the penis and scrotum that might be confused with a sexually transmitted infection. Genital involvement is seen in up to 6.6% male patients with leprosy.<sup>77,78</sup> Patients with lesions over penis in type 1 reaction (reversal reaction) may present as phimosis.<sup>79</sup> Treatment is with WHO-recommended multidrug therapy.

Cutaneous larva migrans is a self-limiting dermatitis commonly known as “creeping eruption,” because of its distinctive feature that the lesion creeps or migrates caused by the presence of a moving parasite in the skin. Cutaneous larva migrans has a worldwide distribution though it is common in the tropics and subtropics. The initial lesion starts as an erythematous itchy papule. Soon, a slightly raised flesh colored swollen lesion about 2–3 mm thick develops and forms linear, serpentine (serpiginous), or bizarre tracts. Very few cases are reported involving male genitalia. Albendazole is used in the dosage of 400–800 mg/day for a period that may vary from 1 to 7 days.<sup>80</sup>

Nonvenereal sclerosing lymphangitis of the penis is an infrequent process that affects the distal lymphatics of this organ. It is characterized by the sudden appearance of a translucent and indurated cord on the coronal sulcus (Fig. 59.13). Its etiology





**Fig. 59.13:** Non-venereal sclerosing lymphangitis of the penis (suggestion of a second corona).



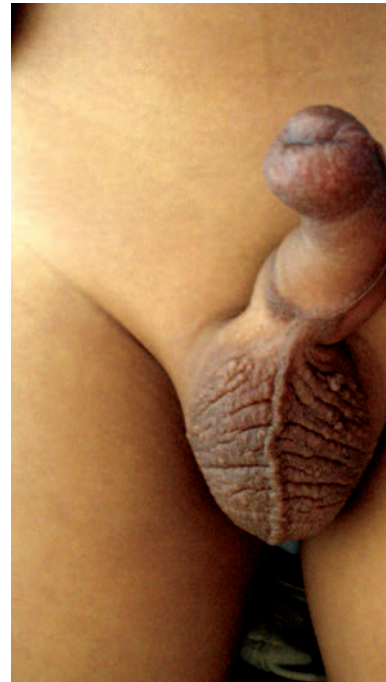
**Fig. 59.14:** Pearly penile papules.

is unknown, although it has been related to microtraumas in the area after intense sexual activity. It is a benign, self-resolving process.

Pearly penile papules are normal, asymptomatic anatomic structures located on the proximal glans penis, often appear as skin-colored 1- to 2-mm, discrete, domed papules around the entire corona (Fig. 59.14). Sometime malformations like lymphangioma can lead to edema of penis and structural deformities including phimosis (Fig. 59.15)

## Role of Skin Biopsy

Patients with balanitis and balanoposthitis may present to various specialties such as dermatology, urology, or STD/GUM clinics. Balanitis is the clinical presentation of varied diseases of the genitalia including infectious lesions, inflammatory and neoplastic conditions, and genital involvement in several dermatological diseases. In most cases, a clinical diagnosis is reached without the need for a biopsy. Nevertheless, penile biopsy is safe and may help to confirm the diagnosis. In a retrospective case-note study from UK on 71 patients referred to the biopsy clinic with persistent genital lesions over a 12-month period, 47 biopsies were performed (71% biopsy rate). Forty-three specimens (92%) were appropriate for histopathological diagnosis. Of these, 15% were lichen planus, 15% LS, 10% psoriasis, and 7.5% each had eczema, Zoon, and non-specific balanitis. The remainder represented a variety of other conditions. In 27 cases (68%), the



**Fig. 59.15:** Lymphangioma circumscripsum scrotum causing saxophone penis.

clinical diagnosis was consistent with the histological result.<sup>81</sup> The average biopsy rate for the diagnosis of non-specific balanitis in 14 UK GUM clinics was reported to be 21.5%.<sup>82</sup> An empirical first treatment, with simple emollients before biopsy, appears to be a safe clinical approach for the treatment of non-specific balanitis. A multidisciplinary approach (GUM physicians, dermatologists, urologists, and histopathologists) could help prevent unnecessary biopsies and improve correlation between clinical and histological diagnosis in these cases. In one series, 60 patients with unresponsive penile dermatoses underwent biopsy, of whom 26% had a non-specific dermatitis, 23% HPV infection, and 15% LS. The original clinical diagnosis was confirmed in 33% of cases and the biopsy was not diagnostic in only 3% of cases.<sup>83</sup>

## Conclusion

The causes of balanitis and balanoposthitis are diverse and include inflammatory dermatological disorders, such as lichen planus, seborrhoeic dermatitis, and psoriasis; premalignant conditions including Bowen disease and penile intraepithelial neoplasia; various infections and contact allergies; and Zoon balanitis. Many balanitides prove difficult to diagnose and any condition, which persists despite treatment, warrants further investigation including penile biopsy to confirm the diagnosis.

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# 60

## Non-venereal Penile Dermatoses

Christopher B. Bunker

### Introduction

Non-venereal skin problems are common in genitourinary clinics. There is a widespread belief that skin diseases of the male genitalia are poorly understood, difficult to diagnose, and unsatisfactory to treat. However, careful dermatological history taking, complete cutaneous examination, and sometimes a skin biopsy usually allow accurate diagnosis and satisfactory medical and surgical management in most cases.

Although stating the obvious, it is worth remembering that the whole skin organ is concerned with sexual expression and activity. The penis is the male structure most commonly deployed in sexual intercourse and it is also the conduit for urinary excretion. The scrotum is the extracorporeal sack for the containment of the testes at the ideal ambient temperature for spermatogenesis. The inguinal folds are intertriginous sites where two layers of skin come into close apposition and function as a part of the hinge between the lower limbs and the trunk. The perineum separates the penis from the anus and the perineal skin is tightly tethered to the underlying tissues.

There are several thousand named skin diseases. This fact is partially explained by considering the pathological possibilities due to the principal morbid processes including neoplasia, inflammation, infection, degeneration, and fibrosis. Their impact on as heterogeneous an organ as the skin with its different cell types, organ structures, and its wide regional, racial, sexual, and physiological variation probably explains this diversity. The genital area differs between the sexes being a good example of regional human variation. The important differences from other sites are that the perineal area is plentifully endowed with functional eccrine and non-functional apocrine sweat glands and holocrine sebaceous glands usually in association with hair follicles but also occurring as free glands (Tyson glands) at some sites such as around the coronal sulcus.<sup>1</sup> These secretions lubricate the hinge between limb and torso, protect the epithelia from irritation, and lubricate the penis for sexual activity primarily in the retraction of the foreskin more than for the penetration of the vagina. The pattern of keratinization of the epithelium also differs throughout

the anogenital area. This is most marked at the mucosal junctions, the prepuce, distal penile shaft, and especially the glans in the circumcised subject. Men have a different pattern of pubic hair when compared with women.<sup>2</sup> The distribution of hair varies widely between men, but in general, the natal cleft, perianal skin, distal penile shaft, prepuce, and glans are devoid of hair. The most common racial variation is pigmentation. The amount of pigment in the skin is related to the amount of melanogenesis and not the number of melanocytes. Melanin synthesis by melanocytes is not only racially determined (constitutive pigmentation), but also induced by sunlight (facultative pigmentation), and circulating and local melanotropic factors (e.g., as part of the cellular response to inflammation). Most races keep the genital skin covered so the later factor is rarely relevant. Physical signs, particularly of inflammation, are harder to detect in deeply pigmented skin. Race may also account for differences in hair type and distribution.

### Normal Variants

Skin tags, naevi, non-viral papillomas, comedones (Fig. 60.1), and hemangiomas may all be regarded as normal variants and are frequently found in the genital area.<sup>1-3</sup> Skin tags are extremely



**Fig. 60.1:** Comedones on shaft of the penis.



**Fig. 60.2:** Seborrheic keratoses on scrotum and shaft of penis.



**Fig. 60.3:** Sebaceous gland prominence.

common in the groins especially of obese men. They may catch on clothing, bleed and get infected. Treatment is by electrocautery or scissor excision and cautery. Seborrheic keratosis, a benign skin tumor, rarely, may occur on the genitals (Fig. 60.2). It may mimic papillomavirus (HPV) infection. Larger, fleshier and more edematous skin tags should arouse the suspicion of Crohn disease. Basal cell papilloma is the most common benign human skin tumor. Single to multiple, flesh colored to black, smooth papule to verrucous plaque, it has a wide differential diagnosis but is frequently mistaken for a viral wart, naevus or bowenoid papulosis. Cullen (1962) reported an incidence of approximately 15% of males having at least one melanocytic naevus (mole) on their genitalia (9.5% in whites; 21.5% in Latins; and 3.5% in blacks).

Sebaceous gland prominence (Fig. 60.3), Tyson glands, sebaceous hyperplasia, ectopic sebaceous glands are all common normal variants of the skin of the scrotal sac and penile shaft but may cause inordinate concern to patients. Pearly, pink, penile papules are common and may be found in up to 15–20% of men, presenting as flesh colored, smooth, rounded papules (1–3 mm) occurring predominantly around the coronal margin of the glans, often arranged in rows or rings (Fig. 60.4).<sup>4</sup> Approximately 35% men will have pearly penile papules in the third decade of their life.<sup>5</sup> A higher prevalence has been reported in black and circumcised men. They can be mistaken for warts by both patients and physicians and are a reason for anxiety for adolescent boys and young adults. In some studies, a relationship with human papillomavirus has been suggested; however, in later work it has been repeatedly confirmed that there is no causal relationship.<sup>6</sup> Histologically, they are angiofibromas. Reassurance usually suffices but cryotherapy or CO<sub>2</sub> laser can be used.<sup>7</sup>



**Fig. 60.4:** Pearly penile papules.

Angiokeratomas (of Fordyce) are less common and are blue to purple, smooth papules on the scrotum or penile shaft that appear and multiply during life (Fig. 60.5).<sup>8</sup> They may cause concern by bleeding. Sometimes they have been misdiagnosed as Kaposi sarcoma or bacillary angiomatosis. The angiokeratomas of





**Fig. 60.5:** Angiokeratomas of Fordyce.

Anderson–Fabry disease (angiokeratoma corporis diffusum) are smaller, less hyperkeratotic pinhead lesions that are found more extensively around the lower limb girdle and upper thighs, from the navel to the knees.

## Circumcision

The prevalence of circumcision in any population reflects racial, religious, and cultural differences. The possible benefits of circumcision may be a lower incidence of inflammatory disease, especially lichen sclerosus and Zoon plasma cell balanitis, as well as protection against sexually transmitted infections including HIV. The foreskin is of variable length and retractability in uncircumcised men. Phimosis refers to partial or complete loss of retractability of the prepuce. It may result from disease processes like lichen sclerosus, lichen planus, and cicatricial pemphigoid.<sup>1,2,9</sup> Paraphimosis describes the situation where the foreskin has become fixed in the retracted state (Fig. 60.6).

## Dermatological Diagnosis

The symptomatic presentation of skin disease is limited. Essentially, patients complain of itch, soreness or pain, a rash, a lump, bump or breach of the skin, or of a problem with hair or nails. The



**Fig. 60.6:** Paraphimosis.

nature of the symptom(s) should be explored, especially the time and space relationships. Patients with anogenital skin complaints are often worried about sexual transmission so a sexual history is vital. The past medical history, especially of skin disease, is important as is the family history. Asthma, hay fever, or eczema in a patient or first degree relative defines atopy. Smoking is a risk factor for cancer of the penis as is poor genital hygiene, but on the other hand the pernicious effects of over-washing with soap are not widely appreciated. Patients may not know what psoriasis is, so it is important to explain. They should be asked about dandruff, cradle cap, warts, and skin cancer. An obsessive drug history is mandatory including that of cough medicines, laxatives, painkillers, and vitamins. When people develop a genital skin problem, they are often frightened that they have contracted a sexually transmitted disease. They then frequently resort to highly unsuitable topical preparations like detergents, disinfectants, and antihistamines. They may have also been misdiagnosed and given an inappropriate prescription by another physician like potent topical corticosteroids or creams containing common allergens. The whole body of the patient should be examined in good light, preferably natural sunlight. It is totally inadequate just to examine the genitalia because the common diagnoses will be reached with the assistance of important clues at other sites. The importance of examining the scalp, brows, eyes, ears, lymph glands, elbows, hands, nails, umbilicus, anus, groins, genitals, knees, feet, toes, retracting the foreskin, parting the gluteal and crural folds, parting the meatal lips, doing a rectal examination, and using a magnifying lens cannot be over-emphasized. Note must be made of the distribution of the rash and its morphology. The site of any lump, bump, erosion, or ulcer must be examined and its morphology defined. It is preferable to draw a diagram and/or obtain a clinical photograph.

Wood's light (a source of ultraviolet light at 360 nm) is helpful in the examination in vitiligo, erythrasma and fungal infections, and rarely porphyria. Skin scraping sent for mycology can be helpful. Occasionally, blood tests or imaging are indicated. Investigations for sexually transmitted diseases (STDs) may be necessary. A skin biopsy is highly informative if the pathologist is given the right information and asked the right question(s). Biopsy cannot be a substitute for clinical diagnosis.

## Pruritus

Pruritus is a cardinal feature of most skin diseases. The response to the sensation of itch is to scratch or to rub and both these actions cause skin morbidity in the form of excoriations, often with secondary infection and impetiginization or lichenification. The important pruritic skin diseases that may affect the anogenital region are listed in Table 60.1.<sup>1,2,10</sup> Itch occurring in the absence of specific diagnostic skin lesions is not usually confined to the genital area but, if so, it should not be labelled as psychogenic until all possible alternative causes have been excluded. The intensity with which itch is sometimes perceived in the anogenital area may be a reflection of the disproportionate cortical representation



**Table 60.1:** Important Causes of Anogenital Pruritus

Causes of genital itching in the absence of clinical findings
Symptomatic dermographism
Contact urticaria
Non-immunological (e.g., mechanical friction of pubic hair, topical substances)
Immunological (latex, body fluids)
Incognito disease
Scabies
<i>Candida</i>
Psoriasis
Drugs
Broad spectrum antibiotics, e.g., tetracyclines
Psychogenic

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of sensory input from the region. It may also be part of more general somatization where there is anxiety about sexual exposure to venereal disease and anogenital cleanliness.

Itching and lichenification around the genitalia and scrotum are common presenting problems. Twenty percent of the population is atopic by definition and this predisposition goes hand in hand with a tendency to itch. Xerosis refers to mildly dry and scaly skin; when more severe the term ichthyosis is used. Two percent of people have psoriasis with a tendency to develop lesions at sites of mild trauma (Köebnerization). These and other diatheses may overlap. The phenotypic possibilities thus created constitute a spectrum of susceptibility to skin disorders. The chief exogenous mechanism is irritation and it may cause problems at vulnerable sites regardless of the phenotype. Irritation may be due to sweat, sebum, friction, desquamated corneocytes, dirt, excreta, sexual secretions, clothing, detergents, toiletries, cosmetics, contraceptives, and topical therapies. It is compounded by maceration and other common afflictions such as piles, constipation, straining at stool, diarrhoea, fecal soiling, incontinence, and overwashing.

## Pediculosis

Pediculosis pubis or public lice (crabs) can cause severe pubic and genital itching with little in the way of physical signs unless the hairs are examined very carefully for nits and the base of individual hairs searched with a hand lens for the louse (1–2 mm in size). Sometimes grey-blue macules, *tache bleu* or *maculae caeruleae*, are seen. Classically, there is an itchy, eczematous eruption with lichenification, excoriations, and secondary impetiginization. In hairy men, the abdomen, chest, axillae, and thighs are also involved. Treatment is with a topical pediculocide such as malathion or permethrin and often also a topical corticosteroid/antibiotic combination. Screening for other sexually transmitted diseases should be offered to the patient and partner(s).

## Scabies

Itch is a predominant symptom of this infestation with the mite *Sarcoptes scabiei*. It can be intense and characteristically keeps patients awake at night. Usually, there is a rash of diagnostic distribution and morphology. Some patients with chronic scabies may have itch in the anogenital region only.

## Urticaria and Dermographism

Dermographism is a form of physical urticaria where rubbing, scratching, and pressure causes an itchy urticarial wheal. It may be a factor in some patients with unexplained genital itching.

## Burning Scrotum Syndrome

In this genital dysesthesia syndrome, patients report itching or burning of the genitalia or scrotum, and complain of persistent or variable redness of the scrotal skin.<sup>1,2,11–13</sup> There may be no signs or a striking erythema. The possibilities of misuse of topical steroids, scrotal rosacea urticaria, dermographism, glucagonoma and of zinc deficiency should be considered. Treatments include avoidance of soap, topical menthol laurumacrogols, lidocaine, dothiepin and systemic antihistamines, tetracyclines, low-dose dothiepin, dosulepin, amitriptyline or gabapentin, steroids, and acupuncture.

## Psychogenic

Dermatological non-disease may be the diagnosis where florid symptomatology is not commensurate with the absence or paucity of any primary dermatological signs. Genital symptoms include itching, excessive redness, burning, and discomfort. In some cases, it is so severe as to prevent the patient from sitting down. Dismorphophobia, depression, and psychosis may be present and attempted or completed suicide is a real risk in such patients.

## Hypopigmentation/Depigmentation

The causes of hypopigmentation and hyperpigmentation are given in Table 60.2.

### POST-INFLAMMATORY HYPOPIGMENTATION AND HYPERPIGMENTATION

Both patterns of pigmentary change are possible after acute inflammation and can contribute to the constellation of physical signs observed in chronic inflammation of the skin. These changes usually appear more pronounced in genetically darker skin. Lichen planus, fixed drug eruptions, and recurrent herpes simplex characteristically cause post-inflammatory hyperpigmentation. Genital trauma, as from a zipper injury, can lead to macular pseudolentiginous lesions on the glans and shaft of the penis. Lichen sclerosus and recurrent herpes simplex are the most common causes of post-inflammatory hypopigmentation. Post-gonococcal and post-syphilitic occurrence has been described.

**Table 60.2:** Causes of Hypopigmentation and Hyperpigmentation

Hypopigmentation or depigmentation
Striae
Vitiligo
Viral warts
Post-inflammatory hypopigmentation
Contact dermatitis
Lichen sclerosus
Herpes simplex
Gonococcal dermatitis
Syphilis
Leukoderma-post-secondary syphilide
Gumma
Post-gummatous atrophic scar
Peyronie disease
Cicatricial pemphigoid
Pseudoepitheliomatous micaceous and keratotic balanitis (PEMKB)
Post-cryotherapy
Electrotherapy
Chemocautery
Laser surgery
Hyperpigmentation
Lentigines
Addison disease
Nelson syndrome
Purpura
Lentiginous melanoma
Post-inflammatory hyperpigmentation
Post-traumatic
Lichen planus
Herpes simplex
Fixed drug eruption

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## VITILIGO

Vitiligo follows loss of melanocytes probably due to autoimmune destruction. The genitalia are very commonly affected in men and it is quite usual for the genitalia to be the only site involved. Wood's light demonstrates the contrast between the normal and the pigmented skin. Vitiligo may be one aspect of a tendency to other organ-specific autoimmune diseases, such as alopecia areata, halo naevus, lichen sclerosus, pernicious anemia, diabetes mellitus, Addison disease, and thyroid disease. There are no effective treatments for vitiligo. However, topical corticosteroids may arrest the progression of the disease in an active phase.

## LEUKOPLAKIA

This is a term used for a white patch or plaque. It is vital to separate vitiligo, post-inflammatory hypopigmentation, lichen sclerosus, warts, and penile carcinoma *in situ* (PCIS). Rare causes of post-inflammatory hypopigmentation include Peyronie disease<sup>14</sup> and PEMKB.<sup>15</sup>

## LENTIGINES

Pigmented macules appear on the glans and shaft of the penis. They are usually benign. Occasionally, they may be large, with irregular edges, multifocal, variegated pigmentary patterns, arousing concern about atypical melanocytic proliferation and acral lentiginous melanoma. Under these circumstances, they should be biopsied.<sup>16</sup> Histology shows increased basal epidermal pigmentation with or without benign lentiginous melanocytic hyperplasia and increase in basal melanocyte number. Penile melanosis is a good term for lesions without lentiginous hyperplasia. The most common site for Peutz–Jeghers multiple blue-brown macules is the oral mucosa but anogenital lesions do occur. It is an autosomal dominant disorder and the usual association is with benign gastrointestinal polyps, but malignant change in the GI polyps occurs in 2–3% of cases. Melanoma rarely can arise on the penis. Irregularly delineated, irregularly pigmented, coalescent macular hyperpigmentation should arouse the suspicion of acral lentiginous melanoma. Melanoma is in the differential diagnosis of all pigmented or amelanotic papules or nodules, but penile melanoma is very rare.

## Inflammatory Dermatoses

Patients complain of a scaly or suppurative rash which may or may not be itchy or sore, spontaneously or with sex. On examination, scaly or non-scaly red patches may be seen. Scales do not readily form on the mucosa. Erythroplakia is an alternative term for a red patch on the mucosa and is in common use in oral medicine. Intertrigo is the name given to any dermatosis occurring in skin folds and is susceptible to secondary infection, especially with *Candida*. Balanitis describes inflammation of the glans penis. Balanoposthitis means inflammation of the glans and prepuce and can be regarded as a special form of intertrigo.

By definition, balanoposthitis does not occur in the circumcised male. The causes of balanoposthitis are given in Table 60.3.<sup>17</sup>

## Eczema and Dermatitis

Eczema is not a diagnosis but refers to the same clinical consequences of several different pathomechanisms in the skin. The symptoms and signs vary with the chronicity of the process. The terms eczema and dermatitis may be used synonymously. Eczema is subdivided into endogenous (e.g., atopic, varicose, seborrheic, etc.) or exogenous (contact eczema).

**Table 60.3:** Causes of Balanoposthitis

<b>Eczema</b>
Exogenous
Allergic contact
Irritant contact
Endogenous
Seborrheic
<b>Psoriasis</b>
<b>Reiter disease</b>
<b>Zoon plasma cell balanitis</b>
<b>Lichen sclerosus</b>
<b>Fixed drug eruption</b>
<b>Candidosis</b>
<b>Streptococcal dermatitis</b>
<b>Staphylococcal cellulitis</b>
<b>Leprosy</b> <sup>17</sup>
<b>Tinea</b>
<b>Most sexually transmitted infections including HPV</b>
<b>Erythroplasia of Queyrat</b>
<b>Kaposi sarcoma</b>

(Reproduced from: Bunker CB. *Male Anogenital Skin Disease*. London: Saunders, 2004)

### IRRITANT CONTACT DERMATITIS

This has been alluded to earlier. Management is directed at re-education and behavior modification. The irritants should be identified and eliminated or reduced. Advice must be given about soap substitutes, moisturizers, towels, and toilet paper. Topical corticosteroid ointments with or without antibiotic and anticandidal agents are employed to control the local disease. Antihistamines by mouth are useful. Topical local anesthetics should be avoided because of the risk of sensitization. Secondary infection may require oral antibiotics. A more acute picture characterized by itch, burning or pain, swelling, erythema, and even vesiculation may occur if chemicals of high irritancy or in high concentration are accidentally or deliberately (not uncommon when patients are frightened about the risk of STDs) used on the genitalia. The differential diagnosis can include HSV or fixed drug eruption. Treatment is with soaks of potassium permanganate, very potent corticosteroid creams (sometimes systemic corticosteroids), and systemic antibiotics.

### ALLERGIC CONTACT DERMATITIS

This comes about by contact-induced type IV cell-mediated hypersensitivity after prior sensitization to the agent concerned. The symptoms are pain, burning or itching and the signs are of acute (erythema, swelling, vesiculation) or chronic (erythema, scaling and lichenification) eczema appearing about a week after first contact with the allergen, or within a few hours or longer if already allergic. Identify the allergen and its likely source

**Table 60.4:** Allergens of Relevance to Anogenital Contact Dermatitis<sup>2</sup>

Methyldibromoglutaronitrile (Euxyl K 400)
Kathon CG
Lignocaine and other topical anaesthetics
Neomycin
Nystatin
Steroid moieties
Rubber <sup>21,22</sup>
Latex condoms <sup>23</sup>
Spermicides <sup>21</sup>

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(Table 60.4), and then achieve its elimination. Patch testing is required. Some cases can persist even after the withdrawal of the allergen. Soap substitutes, moisturizers, and potent topical corticosteroids are required in the acute phase, and sometimes oral antihistamines, antibiotics, and corticosteroids. More immediate symptomatology, acute erythema, and angioedema, suggests a contact urticaria which can occur with some of the rubber constituents of condoms and gloves (Fig. 60.7).<sup>18–21</sup> The reaction can amount to anaphylaxis and is a medical emergency. Therefore, prick or patch testing should be performed cautiously. The most common relevant contact sensitivities are due to rubber, contraceptives, medicaments, and toiletries. An increasing problem has been the development of allergic sensitivity not only to preservatives and antibiotics in dermatologically approved topicals, but also to the corticosteroid moiety itself.



**Fig. 60.7:** Angioedema of penis due to contact sensitivity to condom.



## ATOPIC DERMATITIS

Atopic dermatitis (AD) is a common dermatosis, and is associated with a personal and familial predisposition to dry skin and other atopic diseases such as rhinitis, asthma, and conjunctivitis. Twenty percent of the population may be atopic and up to 10% of children may get atopic eczema presenting as itchy, red scaly lesions on the face and flexures from the age of about 2 months. It can be the cause of considerable morbidity. However, the majority (95% by 15 years) of the children do grow out of the disease. Genital disease due to AD is not uncommon but rarely occurs in isolation. Itching at night, lichenification, excoriations with secondary impetiginization, lichen simplex, and even nodular prurigo may occur. Patients have to be careful about irritation and allergy from condoms and chemical contraceptives. AD is a clinical diagnosis. A biopsy is not necessary. Attention to personal hygiene to avoid irritants such as found in soap and some medicaments is crucial. Similarly, common allergens should be avoided and suspected in cases of unexplained regional exacerbation. Treatment (Table 60.5) depends on using the lowest potency topical corticosteroid capable of containing the disease. Topical calcineurin inhibitors are increasingly useful. Combinations containing antibiotic and anticandidal agents are popular at anogenital sites, but there is a real risk of provoking allergic contact hypersensitivity. Systemic antibiotics are needed frequently for generalized flares or localized complications. Oral antihistamines may be useful at night. Systemic corticosteroids are avoided unless at times of real crisis. Phototherapy is not routinely used for genital skin disease because of the increased risk of skin cancer at this site.

## LICHEN SIMPLEX

Lichen simplex presents as itchy, red patches or plaques of lichenified skin and is common on and around the male genitalia (Fig. 60.8) including the penile shaft and scrotum (Fig. 60.9). The skin may be broken by excoriations and become secondarily impetiginized or colonized by *Candida*. Treatment is mostly medical and only rarely surgical removal of a nodular lesion of lichen simplex may be required.<sup>22</sup>

**Table 60.5:** Treatment of Atopic Dermatitis

Moisturizers and soap substitutes <sup>2</sup>
Topical corticosteroids (+ antibiotic/anticandida)
Oral antibiotics
Oral antihistamines
Systemic corticosteroids (oral, I/M, ACTH)
UVB phototherapy
Psoralens + UVA (PUVA) phototherapy
Azathioprine
Cyclosporin

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**Fig. 60.8:** Thick, lichenified skin of scrotum in lichen simplex chronicus.



**Fig. 60.9:** Lichenification and edema of penis and scrotum in lichen simplex chronicus.

## SEBORRHEIC DERMATITIS

Seborrheic dermatitis is a very common pattern of eczematous disorder that probably results from a diathesis of abnormal hypersensitivity to the normal commensal cutaneous yeast,



**Fig. 60.10:** Erythematous scaly lesions of seborrheic dermatitis on glans and prepuce.

*Pityrosporum ovale*. Patients complain of a red scaly appearance of the skin (Fig. 60.10). Itching is mild, there is slight erythema, slight to moderate scaling and often folliculitis. The scalp, ears, glabella and brows, nasolabial folds, axillae, chest, and back are also commonly involved as are the groins and penis. Careful examination of these sites supports the diagnosis. Some patients may also have a tendency to develop psoriasis (sebopsoriasis). Their signs may be more florid and other physical signs of subtle or overt psoriasis may be seen on careful assessment. Seborrheic dermatitis is a cutaneous manifestation of HIV infection when it can be very severe and generalized even amounting to erythroderma. Its severity is increased with CD4+ lymphocyte counts below 100/ $\mu$ L. Scrapings can be examined for fungi to exclude tinea and to demonstrate *Pityrosporum* spp. in large numbers. Treatment may not be required by all. However, treatments that suppress the commensal *Pityrosporum* load and reduce irritation and eczematization can be successfully and safely used long term. These include topical antifungals, such as clioquinol, nystatin, and imidazoles, as ointments, creams, lotions, or shampoos. Mixtures of the same agents with mild and moderately potent topical corticosteroids can be used alongside emollients and soap substitutes. Topical calcineurin inhibitors are also effective. In severe cases, such as with concomitant seborrheic folliculitis or in HIV, a course of, or continuous, oral ketoconazole and/or an oral tetracycline might be indicated.

## Psoriasis

Approximately 2% of the population is said to have psoriasis but the diathesis may be much more widespread depending

on the clinical weight given to hesitant and uncertain family histories, vague personal histories of prior rashes, hair and nail problems, and the interpretation of mild scaling of the scalp, ears, elbows, knees, hyperkeratosis of the palms and soles, and nail dystrophy, and pitting. Currently, psoriasis is regarded as a disorder of primary immunodysregulation determined both by a genetic predisposition and environmental triggers (perhaps to streptococcal or other superantigens). These cause the vascular changes, leukocyte infiltration, and epidermal hyperproliferation that are the pathological hallmarks of the disease. The clinical manifestations of psoriasis are of variably itchy, silvery-scaled, erythematous, patches or plaques, which may be guttate, or nummular, in a symmetrical pattern, especially on extensor surfaces. Sometimes a pustular type is seen especially on the palms and soles. The scalp, ears, and umbilicus (and face in sebopsoriasis) are involved, as is the anogenital skin, especially the sacrum, buttocks, pubic mound, shaft of penis, and the glans of the circumcised male (Fig. 60.11). The Köebner phenomenon, which is defined as the appearance of a skin disease at the site of trauma or of another skin disorder, may contribute to this distribution. It is worth stressing that anogenital sites may be the only involved site. Nail changes in the form of pits, onycholysis, and subungual hyperkeratosis may accompany psoriasis. Inverse pattern psoriasis refers to the appearance of the disease on intertriginous skin in the natal cleft, the gluteal folds, the groins, under the dependent, flaccid penis and in the preputial sac and on the glans of the uncircumcised male (where the epithelium is also unkeratinized). Inordinate itch would make one suspicious



**Fig. 60.11:** Psoriasis of glans and shaft of penis.



of tinea and a scraping should be examined and cultured for fungi. Soreness supervenes with superinfection, especially with *Candida*. Some drugs may trigger or worsen psoriasis, including lithium, beta-blockers, antimalarials, and angiotensin-converting enzyme inhibitors. Psoriasis may worsen or appear for the first time in the HIV-infected patient. Pustulosis may predominate and occasionally psoriasis is the cause of an erythroderma. Again anogenital lesions are common and frequently disabling. Usually, the diagnosis is clinical but a biopsy might be necessary for the solitary mucosal lesions in the uncircumcised, where Zoon balanitis and erythroplasia of Queyrat enter the differential diagnosis. Topical treatment relies on emollients, soap substitutes, corticosteroids combined with antibiotic and antifungal agents or weak tar solutions. Strong, crude tar preparations should be avoided. Dithranol, because of its irritant potential, is usually avoided in this region. The vitamin D analog calcipotriol can be helpful as can calcineurin inhibitors. Severe anogenital, inverse psoriasis can be an absolute indication for systemic treatment with drugs like methotrexate or cyclosporin. Phototherapy is contraindicated because of the risk of genital cancer.

### Reiter Disease

Reiter disease or syndrome is part of the same continuum as psoriasis in genetically predisposed individuals. Reiter syndrome is defined as arthritis, urethritis, and conjunctivitis.

It is precipitated by non-specific urethritis or bacillary or amoebic dysentery and associated with HLA B27. The clinical features, radiological signs, diagnosis, and management are discussed in Chapter 65. Skin lesions in Reiter syndrome may be similar to those of psoriasis. Classically, patients with Reiter disease may have thickened yellow palms and soles with a cobblestone appearance with or without pustular lesions (keratoderma blennorrhagica) and involvement of the penis (circinate balanitis, Fig. 60.12); but they may also have any of the features of psoriasis described above. Arthritis (oligoarticular) is an important component. Penile lesions have the same histopathology as psoriasis. Reiter disease has been reported with increased frequency in patients with AIDS

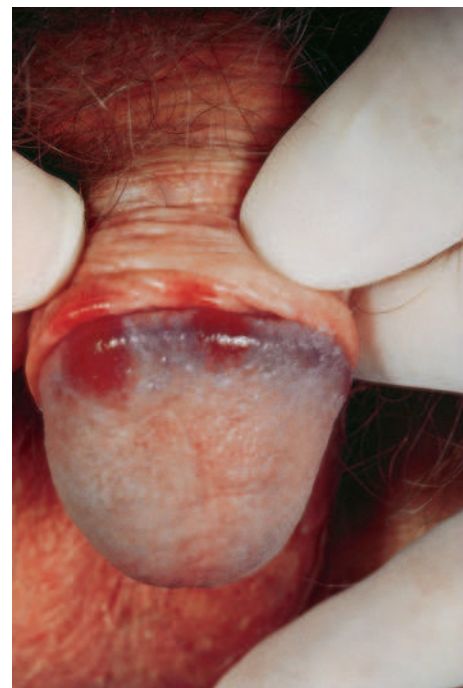


**Fig. 60.12:** Circinate balanitis.

and also in the earlier stages of HIV infection in its classical or incomplete form. Treatment is similar to that for psoriasis. Genital lesions seem to be curiously responsive to topical calcineurin inhibitors. Oral retinoids are useful especially in HIV-infected patients.

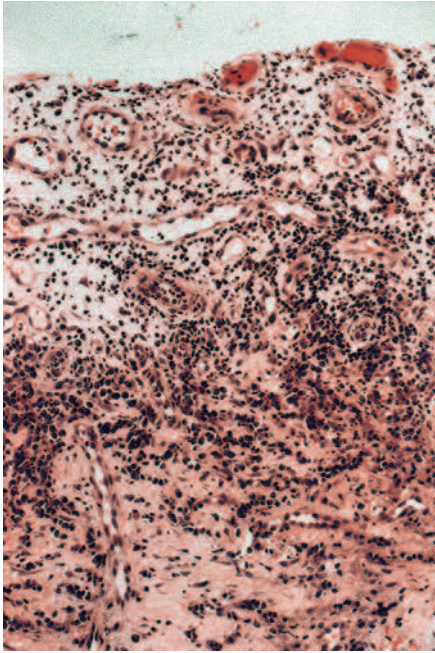
### Zoon Plasma Cell Balanitis

Zoon plasma cell balanitis is a disease of the uncircumcised man. It does not occur on the keratinized penile shaft or foreskin of an uncircumcised men and is not seen in circumcised men at all. However, it has also been reported to afflict the vulva, mouth, lips, and epiglottis. The presentation is of indolent and relatively asymptomatic, well-demarcated, glistening, moist, shiny, bright-red or brown patches seen anywhere over the glans and prepuce (Fig. 60.13). Dark red stippling, "cayenne pepper spots," is due to hemosiderin deposition. Solitary or multiple lesions of differing sizes (guttate or nummular) may be seen, which characteristically "kiss." The etiology of Zoon balanitis is unknown, but its occurrence in the uncircumcised suggests an irritant or hypersensitive response to retained smegma (desquamated keratinocytes and secretions), commensal and/or opportunistic micro-organisms and urine. Chronic infection with *Mycobacterium smegmatis* has been postulated. Trauma, heat, poor hygiene, and mild urinary incontinence may be the factors. The most important differential diagnoses are erythroplasia of Queyrat or intraepithelial carcinoma *in situ* of the penile mucosa, erosive lichen planus, Kaposi sarcoma, psoriasis, and seborrheic



**Fig. 60.13:** Zoon balanitis. Glans and prepuce. "Butterfly" or "kissing" lesions. Reproduced with permission from: male anogenital skin diseases, Ref. 2.





**Fig. 60.14:** Zoon balanitis. The key features are erosion, ulceration, vascular ectasia and congestion with no intact epidermis on the surface. Beneath this there is edema and a band-like chronic inflammatory infiltrate, which is heavily populated by plasma cells. Some fibrosis is also apparent. Reproduced with permission from: Male anogenital skin diseases, Ref. 2.

dermatitis. Others include secondary syphilis (all patients should be screened for sexually transmitted disease), tinea, contact dermatitis, and fixed drug eruption. It is important to realize that Zoon balanitis may not be a primary dermatosis but rather a reactive process indicative of a dysfunctional foreskin.<sup>1,2,23</sup> Careful examination for an underlying primary dermatosis should be carried out. A biopsy is advised in most cases and the pathologist should be asked to look for concomitant disease like lichen sclerosis. Zoon balanitis has distinctive histologic findings. Epidermal atrophy with complete effacement of the rete ridges is present. Ulceration may occur. Diamond-shaped “lozenge keratinocytes” are common with uniform intercellular spaces termed watery spongiosis. A dense lichenoid sub-epidermal infiltrate composed largely of plasma cells is characteristic (Fig. 60.14). Erythrocyte extravasation and hemosiderin deposition are often noted. Although the condition may improve with enhanced hygiene and the intermittent application of mild or potent topical corticosteroid (+ antibiotics and anticandidals), and topical calcineurin inhibitors. Zoon balanitis usually persists or relapses. Definitive curative treatment is circumcision.

## Lichen Sclerosis

Penile lichen sclerosis may be asymptomatic. However, diverse, often vague, symptomatology is usually encountered. Patients may describe itching, burning, bleeding, hemorrhagic blisters,



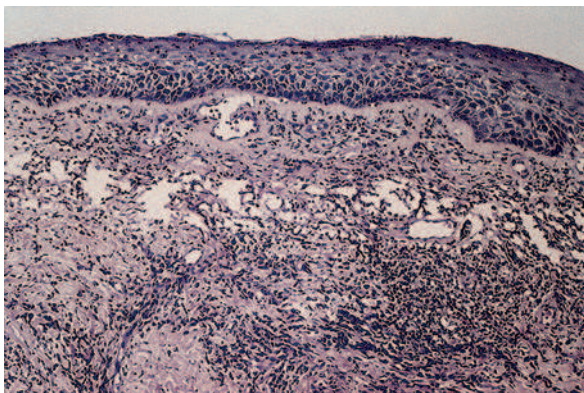
**Fig. 60.15:** Atrophic, white patches of genital lichen sclerosis.

discomfort with urination and narrowing of the urinary stream. They may be concerned about the changing anatomy of their genitalia. The predominant symptomatology is of difficulty with sexual intercourse. The usual cutaneous presentation of lichen sclerosis is of atrophic white patches or plaques (Fig. 60.15). However, lilac, slightly scaly patches with telangiectasia and sparse purpura, bullae, erosions and ulceration may be encountered. Other presentations are phimosis, paraphimosis, urinary retention, and even renal failure. Anogenital lichen sclerosis is more common than extragenital or oral disease. Rarely, there may be concomitant involvement of these sites. In adults, anogenital lichen sclerosis is said to be about ten times more common in women than men. Perianal disease is very rare in the male. Lichen sclerosis may be much more frequent than is generally supposed in young boys. Persistent primary phimosis or the secondary development of phimosis in a previously retractable foreskin should be viewed with suspicion: some, many or most of such cases will be due to lichen sclerosis. Whereas posthitis xerotica obliterans refers to chronic damage to the prepuce by lichen sclerosis, balanitis xerotica obliterans (BXO) is a more frequently encountered term describing severe damage from long-standing, sometimes undiagnosed, unchecked disease. BXO can be a consequence of other scarring dermatoses such as lichen planus and cicatricial pemphigoid. The evidence indicates that male genital lichen sclerosis (MGLSc) is due to chronic occluded exposure of susceptible epithelium to urine. MGLSc never occurs in men who were circumcised at birth; is associated with trauma, instrumentation, genital jewelry (piercing), and gross anatomical abnormalities (e.g., frank hypospadias); recurs in grafts; and never causes perianal disease (in striking contradistinction to women, the male perineum is never chronically exposed to urinary irritation).<sup>1,2</sup> The arrangement of the distal urethra, navicular fossa, and meatus has evolved to function as a low-pressure valve. The embryology is complicated, and a wide variation in naviculomeatal valve structure and function is revealed by meticulous clinical assessment. Many men presenting with genital lichen sclerosis mention dribbling after voiding and have abnormal naviculomeatal morphology on examination. In these men, urine dribbling from the meatus after the prepuce has

been replaced following voiding will spread widely between the juxtaposed mucosal surfaces. Occlusion and the phenomenon of koebnerization create the inflammation.

Female genital lichen sclerosis seems to spare non-cornified stratified squamous epithelium and women do not have urethral disease. In men, susceptibility to the irritant effects of urine may be due to variability in the epithelialization of the mucosa of the distal urethra and navicular fossa, as well as their dysfunction as a valve. The definition of mucosa is controversial but indubitably the proximal penile urethra possesses a true mucosa, while the circumcised glans certainly does not, the uncircumcised glans and inner prepuce probably do not, and the outer prepuce does. There are transition zones between true urothelium and true skin. Just as there is wide variability in the size and shape of the navicular fossa, there is probably variability in the site of the epithelial transition zones, the degree of keratinization of the glans, the length and, thus, surface area of the foreskin, and the disposition of adnexa. Perhaps urethral lichen sclerosis eventuates because the transition to stratified keratinizing squamous epithelium occurs and/or urethral mucus glands are lost, too proximally, thus rendering the epithelium focally susceptible to the pernicious irritant effects of urine.<sup>1,2,24,25</sup> However, patients with lichen sclerosis, especially women, have an increased incidence of organ-specific autoantibodies and autoimmune disease. In male genital lichen sclerosis, there is an increased frequency of several class II antigens including HLA DQ7 which also occurs more frequently in women with lichen sclerosis. One study has found HPV (types 6, 16, and 18) in 70% of boys with lichen sclerosis, but the overall clinical impression of lichen sclerosis is that it is not a communicable disease. Most cases of lichen sclerosis can be diagnosed clinically.

Sometimes lichen planus and cicatrizing pemphigoid may raise diagnostic difficulties. If there is clinical doubt, then a biopsy should be done. A biopsy is mandatory if the lesion or a part



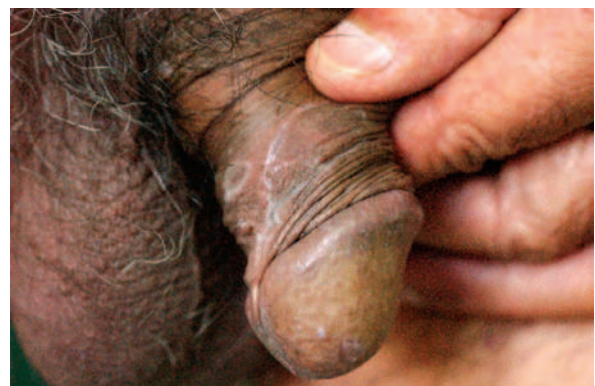
**Fig. 60.16:** Lichen sclerosis showing the typical small vessel dilation within the bland and loose edematous hyaline stroma beneath the epidermis and, beneath that, patchy aggregates of chronic inflammatory cells. Courtesy: Nick Francis, London, UK. Reproduced with permission from: male anogenital skin diseases, Ref. 2.

is eroded or verrucous. Histology initially shows a thickened epidermis, followed by atrophy and follicular hyperkeratosis. This overlies an area of edema with loss of the elastic fibres and alteration in the collagen, which in turn overlies a perivascular band of lymphocytic infiltration (Fig. 60.16). Hemorrhagic vesicles occur when the edema causes detachment of the epidermis with capillary erosion and extravasation of blood. Very potent topical corticosteroid used under supervision is an effective treatment. This appears to induce remodeling of the affected mucosa, relieve phimosis, improve the histological signs, and save the organ from circumcision. Confounding secondary candidal and bacterial infection should be treated. Testosterone propionate ointment and oral stanozolol have been used to debatable effect. Topical calcineurin inhibitors should not be used.<sup>26</sup> Carbon dioxide laser treatment for lichen sclerosis has been reported.

Frenuloplasty, meatotomy, or a sophisticated plastic repair may be necessary. Even if disease involves non-preputial sites it can regress following circumcision. But lichen sclerosis can persist or recur. Squamous cell carcinoma of the penis is the worst possible complication of lichen sclerosis. The risk is possibly less than for vulval lichen sclerosis. A risk of 2–12.5% is suggested by the literature, depending on length of follow-up; the latent period may be 1–3 decades. Verrucous carcinoma (Buschke–Löwenstein tumor) has been associated with previous lichen sclerosis.<sup>1,2</sup> It is not known for certain what impact medical and surgical treatment has on the subsequent incidence of penile cancer. Patients should be followed up long term, especially if circumcision has not been performed or if symptoms persist or recur after any modality of treatment.

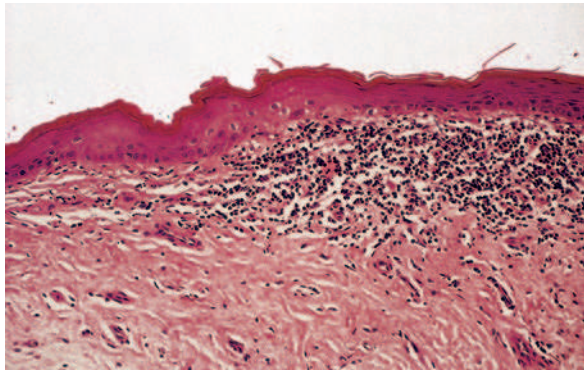
## Lichen Planus

Lichen planus is a common inflammatory dermatosis that has a particular predilection for the mucosae and can involve these sites in isolation. The classical extragenital eruption is often intensely itchy and symmetrical, manifesting as flat-topped, polygonal, purple papules, coalescing to form annules and plaques and surtopped by fine, lacy scales called Wickham striae (Fig. 60.17). An aggressive form may lead to a scarring folliculitis of



**Fig. 60.17:** Annular lesions of lichen planus showing Wickham striae.





**Fig. 60.18:** Lichen planus. A medium power view of penile skin showing flattening of the wheaty architecture and underlying lichenoid chronic inflammatory infiltrate with interface inflammation of the basal epidermal layer and associated degeneration. Courtesy: Nick Francis, ICM, London, UK. Reproduced with permission from: male anogenital skin diseases, Ref. 2.

the scalp and a permanent nail dystrophy. Lichen planus can present in the anogenital area, like the classical disease at other sites, as itchy, red-purple papules and also as patches or plaques. Occasionally, an erosive form is encountered and this can be extremely symptomatic leading to severe male dyspareunia. The itchy, monomorphic, flesh-colored, micropapular form, lichen nitidus has a predilection for the penis but rarely in isolation. Most cases of lichen planus are self-limiting, although some patients relapse and remit. Post-inflammatory hyperpigmentation can exist for months or years. Chronic mucosal erosive lichen planus is associated with a risk of progression to squamous cell carcinoma, but most reports concern oral lichen planus. Squamous carcinoma may complicate chronic hypertrophic lichen planus of the lower leg but has also occurred in the context of hypertrophic lichen planus of the glans penis. A biopsy is, therefore, sometimes performed for diagnostic purposes (Fig. 60.18) but is more importantly done in the follow-up of the rare cases of chronic genital disease, where development of ulcerative or verrucous features leads to concern about the development of squamous cell carcinoma. Potent and very potent topical corticosteroids usually suffice for treatment. Patients are told to continue with the treatment until the lesions are non-itchy and flat. They are warned about post-inflammatory hyperpigmentation. Intralesional and systemic corticosteroids are sometimes exhibited for severely itchy disease and erosive orogenital involvement. Topical and oral cyclosporin have been used. Circumcision can cure erosive genital disease presumably by abolishing köebnerizing forces.<sup>27</sup>

### Hailey–Hailey Disease (Benign Familial Pemphigus)

Hailey–Hailey disease is an autosomal dominant disorder of keratinocyte adhesion with gradual onset in young adulthood and a tendency to improvement with age. The clinical features of this disease are moist, crusted plaques or scaly patches studded with pustules and warty papules involving the flexures. Very rarely papular

plaques similar in appearance to genital warts have been reported. The differential diagnosis in the groins is of an intertrigo with Darier disease. The diagnosis is confirmed histologically. The mainstay of treatment is topical corticosteroids and topical antibiotics. Radiotherapy (Grenz rays and electrons), etretinate, and acitretin have also been used successfully. Dermabrasion, excision with grafting and CO<sub>2</sub> laser ablation are other options.

### Darier Disease (Keratosis Follicularis)

Flexural disease is mild in most patients but does occur in the vast majority. The lesions can be very sore and malodorous. The intertriginous features are similar to those of Hailey–Hailey disease. Nearly all patients will have keratotic papules in seborrheic areas, palmar pits, and nail changes in the form of dystrophy, fragility, Union Jack nails—red, white and blue streaks, V-shaped terminal nicks. Sunlight is a known provocation but usually clinically irrelevant in terms of genitocrural disease and bacterial or herpetic superinfection, well-recognized. Biopsy confirms the diagnosis. Topical treatment for Darier disease follows the same lines as for Hailey–Hailey disease. However, a very useful modality in the former is the use of oral retinoids, such as isotretinoin and acitretin. Use of these agents is limited in women of child-bearing potential because of fetal teratogenicity and the risk of side effects due to the hypervitaminosis. A syndrome (especially diffuse idiopathic [misnomer] skeletal hyperostosis). Local radiotherapy to flexural sites has helped some patients and recently CO<sub>2</sub> laser ablation has been advocated.

### Fixed Drug Eruption

Fixed drug eruptions (FDE) are red, swollen plaques sometimes with central blister formation, erosion, and ulceration (Fig. 60.19). The symptoms are itch or burning. The genitalia are classical sites for this, as are the face and extremities. Healing is with post-inflammatory hyperpigmentation. On first exposure, the eruption can take 1–2 weeks to appear, but subsequently appears just a few hours to a few days after ingestion. Recurrence occurs at the same site each time the drug is exhibited, and such rechallenge can be used as a diagnostic test. Causes of FDE



**Fig. 60.19:** Bullous fixed drug eruption.





**Fig. 60.20:** Intertriginous lesions of erythrasma.

are tetracyclines, phenolphthalein, sulfonamides, barbiturates, quinine, and papaverine. A biopsy can confirm the clinical diagnosis. Treatment obviously centers around identification and withdrawal of the offending agent. Very potent topical corticosteroid treatment used in the acute phase may limit the symptomatology and long-term damage.

### Erythrasma

Velvety, red, superficially scaly plaques are found extending symmetrically from the groins onto the upper thighs. In the inguinal folds, erythrasma is an intertrigo and may be macerated and eroded (Fig. 60.20). It is not usually very itchy but can be slightly sore in the groins and may have been present for years. Other sites of predisposition include the axillae and toe web spaces. The causative organism is a gram-negative rod/coccus, *Corynebacterium minutissimum*. Erythrasma is a clinical diagnosis confirmed by coral pink fluorescence under an ultraviolet source (Wood's light), bacteriology, and exclusion of tinea cruris. Topical treatment with clindamycin, erythromycin or an imidazole is effective, but a course of oral erythromycin is definitive and effective at several sites simultaneously. However, erythrasma is prone to recur.

### Candidosis

Candidosis (thrush) presents as an intertrigo or balanoposthitis. Burning and soreness are more likely than itch. Coalescent red patches or plaques involve the folds often with superficial erosions. Pustulosis may extend out onto the skin of the abdomen, buttocks or thighs from the irregularly margined intertriginous lesions. *Candida* of the penis, which appears to have a prevalence of about 10% of that of vaginal candidiasis, has attracted very little research interest. Some have argued that primary *Candida* of the penis does not occur in the immunocompetent man. *Candida* is frequently found as a secondary pathogen in anogenital dermatoses. Eliciting the signs of candidosis does not preclude a thorough clinical search for an underlying dermatological or medical cause. This is because the signs due to *Candida* may be more florid than the underlying cause. Medical causes (Table 60.6) include diabetes mellitus, iatrogenic immunosuppression, and systemic antibiotic treatment. Although it is indisputable

**Table 60.6:** Medical Causes of Candidosis<sup>2</sup>

Obesity
Diabetes mellitus
HIV infection
Iron deficiency
Cushing syndrome
Iatrogenic immunosuppression
Debilitating infection or cancer
Urinary incontinence
Systemic antibiotic treatment, etc.

(Reproduced from: Bunker CB. *Male Anogenital Skin Disease*. London: Saunders, 2004).

that oropharyngeal candidiasis is almost invariably found in HIV infection, genital disease is not. It may be overlooked in the face of more pressing symptomatology in other sites or systems. Diagnosis is clinical and supported by direct demonstration of the budding forms of the yeast and pseudohyphae (visualization is enhanced in a potassium hydroxide preparation by a drop of India ink under the cover slip) and microbiological culture.

Underlying disease should be identified and treated and predisposing factors rectified. Treatment includes topical nystatin, clioquinol or an imidazole, often very usefully combined with hydrocortisone or a moderately potent corticosteroid. An oral azole (imidazole or triazole) like itraconazole, fluconazole, ketoconazole may also be indicated. Many HIV-positive patients may be required to take long-term azole antifungals orally.

### Tinea

Tinea or ringworm (Fig. 60.21) refers to superficial dermatophytosis. *Trichophyton rubrum* is the most common



**Fig. 60.21:** Annular lesion of tinea on shaft of the penis.

species responsible. Tinea is a common disease of the pelvic girdle especially of the groins and is not always spread from the feet. People with tinea manuum or unguium can spread it to the groins or feet because they are common sites of chronic itch. Tinea cruris is itchy, and diagnosed in the presence of red-brown, scaly patches with raised, redder edges extending out of the groins and onto the abdomen, buttock and down the thighs. Because of the site, annular lesions are not obvious but can be imagined. Unfortunately, clinical diagnosis is not always straightforward because many patients have been previously misdiagnosed and/or partially treated with topical corticosteroids plus or minus topical antifungal agents. Tinea incognito is the expression given to the presentation in the previously corticosteroid-treated patient where the symptom of itch and the signs of inflammation including the redness, the scale, and the well-demarcated often scalloped, elevated active edge have been suppressed. There will, however, be abundant fungal hyphae, which makes the diagnosis by microscopy (potassium hydroxide preparation of a skin scraping) much easier. Patients partially treated with topical antifungals are harder to diagnose because the signs are attenuated, and there will be few hyphae making microscopy difficult. Culture may be inhibited by the presence of the drug in the specimen. Reevaluating the patient after a few days abstention from topical treatment is often advisable. Other problems are the concomitant presence of erythrasma<sup>28</sup> and the rare occurrence of tinea on the glans penis causing itch, pain and producing an erythematous patch that also involves the scrotum.<sup>29–31</sup> Wood's light examination is sometimes helpful in the diagnosis of more exotic fungal infections and for excluding erythrasma. For treatment, anogenital dermatophytosis often requires oral treatment with griseofulvin, terbinafine or itraconazole. Topical treatments often fail because of the anatomical complexity of the area; difficulty in sustaining complete, protracted, regular coverage of the whole area with a cream or ointment; and because there may be mycosis of feet or hands, toe or finger nails.

## Erosions and Ulcers/Blisters and Vesicles

Causes of erosions, ulcers, and vesicles and bullae have been listed in Table 60.7.

## Genital Trauma

The genitals may be traumatized by sexual activity. The penis is very vascular and hematoma formation is not rare. Sex aids can result in abrasions, eczema, and ulceration.

The penis may be incarcerated by ring device, rubber bands or hair, and strangulation, necrosis and autoamputation may follow. Seriously mentally ill patients have been known to mutilate their genitalia, as have transvestites, but non-psychotic genital self-mutilation can also occur. Australian aborigines slit the penis and open the urethra ventrally, creating a hypospadias and this is called subcision. The penis may

**Table 60.7:** Causes of Erosions, Ulcers, and Vesicles and Bullae<sup>2</sup>

Causes of erosions	Causes of ulcers
<ul style="list-style-type: none"> <li>Trauma and artefact</li> <li>Excoriated eczema and other pruritic dermatoses e.g., scabies, Hailey–Hailey disease</li> <li>Pemphigus</li> <li>Pemphigoid</li> <li>Dermatitis herpetiformis</li> <li>Lichen planus</li> <li>Lichen sclerosus</li> <li>Zoon balanitis</li> <li>Erythema multiforme</li> <li>Fixed drug eruption</li> <li>Intertrigo</li> <li>Inverse pattern psoriasis</li> <li>Erythrasma</li> <li>Streptococcal dermatitis</li> <li>Candidosis</li> <li>Tinea</li> <li>Gonorrhea</li> <li>Secondary syphilis</li> <li>Mucous patch (herpetiform)</li> <li>Herpes simplex</li> <li>Herpes zoster</li> <li>Erythroplasia of Queyrat</li> <li>Kaposi sarcoma</li> </ul>	<ul style="list-style-type: none"> <li>Trauma and artefact</li> <li>Aphthae</li> <li>Behçet disease</li> <li>Hidradenitis suppurativa</li> <li>Crohn disease</li> <li>Pemphigus</li> <li>Necrobiosis lipoidica</li> <li>Fixed drug eruption—nicorandil</li> <li>Pyoderma gangrenosum</li> <li>Calciphylaxis</li> <li>Hypereosinophilic syndrome</li> <li>Ecthyma gangrenosum</li> <li>Herpes simplex</li> <li>Gonorrhea<sup>32</sup></li> <li>Syphilis</li> <li>Primary chancre</li> <li>Snail track ulcers</li> <li>Yaws</li> <li>Chancroid</li> <li>Donovanosis (lymphogranuloma inguinale)</li> <li>Lymphogranuloma venereum</li> <li>Fournier gangrene</li> <li>Tuberculosis/tuberculide</li> <li>Amoebiasis</li> <li>Filariasis</li> <li>Histoplasmosis</li> <li>Actinomycosis</li> <li>Langerhans cell histiocytosis</li> <li>Paget disease</li> <li>Basal cell carcinoma</li> <li>Squamous carcinoma</li> <li>Verrucous carcinoma</li> <li>Sweat gland carcinoma</li> <li>Kaposi sarcoma</li> <li>Leukemia</li> </ul>
Causes of vesicles and bullae	
<ul style="list-style-type: none"> <li>Acute contact dermatitis</li> <li>Erythema multiforme</li> <li>Dermatitis herpetiformis</li> <li>Lichen planus</li> <li>Lichen sclerosus</li> <li>Fixed drug eruption</li> <li>Pemphigoid</li> <li>Pemphigus</li> <li>Herpes simplex</li> <li>Herpes zoster</li> </ul>	

also be traumatized by external urinary devices employed to counter urinary incontinence.

## Dermatitis Artefacta

Dermatitis artefacta focalized to the penis is sometimes encountered. Dermatitis artefacta at other sites is recognized by dermatologists as unexplained erosions or ulcers that fail to heal or inexplicably breakdown despite treatment. The lesions are often geometrical, angulated or rectilinear. Sometimes they are induced by needles, knives, instruments, and cigarettes. Extraneous foreign material may be introduced into the skin. The psychological ambience of *belle indifférence* may be present. There may be depression, but rarely is a major psychiatric illness present. Confronting the patient with the suspected diagnosis is widely regarded as dangerous because of the risk of suicide. Management must be medically and psychologically supportive. Antipsychotic medication such as pimozide may be successful if accepted by the patient.



## Aphthae

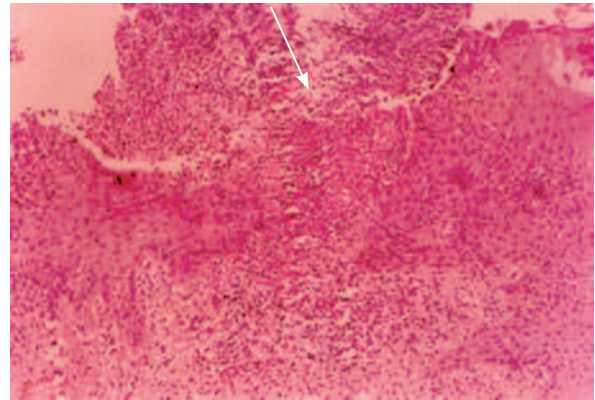
Aphthous ulceration of the penis and scrotum does occur, but this is not an acceptable diagnosis in the perianal skin or without overt exclusion of sexually transmitted diseases and other causes of genital ulceration, especially Behçet syndrome.<sup>32</sup> This is completely different from oral aphthae where a clinical diagnosis is acceptable clinical practice. The causes of aphthae are obscure. The histology is non-specific. Treatment is with topical corticosteroid/antibiotic/anticandida combinations.

## Behçet Disease

Behçet disease<sup>32,33</sup> is an inflammatory disorder of unknown cause, characterized by recurrent oral aphthae, genital ulcers, uveitis, and skin lesions. Complex aphthosis,<sup>34</sup> which is considered to be a *forme fruste* of Behçet disease, is defined as the presence of almost constant, multiple (>3) oral or oral and genital aphthae in the absence of systemic manifestations. According to the International Study Group<sup>35</sup> criteria, Behçet disease is diagnosed in the presence of recurrent oral ulceration with any two of the following criteria, i.e., recurrent genital ulceration (Fig. 60.22), uveitis or retinal vasculitis, papulopustular lesions or erythema nodosum or acneiform lesions and a positive pathergy test. There can be involvement of central nervous, gastrointestinal, cardiovascular, pulmonary, and musculoskeletal systems, and kidneys. The pathogenesis of Behçet disease and complex aphthosis is mediated by a combination of factors involving immune dysregulation, inflammatory cytokines and infectious agents in a genetically predisposed individual (HLA B51). The histologic features of Behçet disease are characterized by vasculitis and thrombosis



**Fig. 60.22:** Scrotal and penile ulcers of Behçet disease.



**Fig. 60.23:** Histology of Behçet disease showing leukocytoclastic vasculitis and a dense lymphocytic infiltrate in the dermis.

(Fig. 60.23). The vasculitis may be leukocytoclastic or a lesser degree of neutrophilic vascular reaction with no fibrinoid necrosis. The differential diagnosis of the systemic features of Behçet disease is systemic lupus erythematosus (SLE), relapsing polychondritis (MAGIC syndrome), familial Mediterranean fever, and Reiter syndrome. Treatment is with topical or intralesional corticosteroids, colchicine, thalidomide, rebamipide and dapsone for mild to moderate mucocutaneous lesions. Immunosuppressive drugs (such as systemic steroids and azathioprine) or biological response modifiers (such as infliximab, etanercept, and adalimumab) are indicated for severe mucocutaneous lesions, severe ocular lesions, and in cases of systemic involvement.<sup>33</sup>

## Hidradenitis Suppurativa

Painful genital skin involvement with fibrous bridges, comedones, folliculitis, furunculosis, deep discharging sinuses, nodules, cysts, and scars in the groins (Fig. 60.24) and axillae is pathognomonic.<sup>1,2</sup> The disease may involve the natal cleft and buttocks. It is more common in black subjects. It affects the axilla preferentially in women and the perineum in men. Many patients will also have severe conglobate acne. The morbidity of hidradenitis can be very severe, interfering with sitting, sleeping, walking, defecation, and



**Fig. 60.24:** Discharging sinuses and ulcers of hidradenitis suppurativa.



sexual activity, so depression is common. Hidradenitis suppurativa is considered by some to represent apocrine acne. The role of endocrine factors is unknown. Occlusion leads to comedone formation and purulent infection due to secondary infection with gram-negative and gram-positive organisms. Chronicity carries a risk of squamous cell carcinoma. Hidradenitis is a clinical diagnosis. Swabs should be taken for bacteriological evaluation and to guide therapy.

Rarely, a biopsy may be necessary to exclude carcinoma or Crohn disease. Perineal Crohn disease mimics hidradenitis with its granulomatous inflammation, ulceration, and fistula formation, but it is less painful, the axillae are uninvolved, and it is rare for patients to be free of overt gastrointestinal symptoms. Oral antibiotics such as erythromycin, flucloxacillin, ciprofloxacin, metronidazole, and topical antiseptics offer the lynchpin of management. In men, hormonal manipulation with antiandrogens such as cyproterone acetate is an option, as it is in women. Oral prednisolone can be used as alongside antibiotics to control intercurrent exacerbations. Oral isotretinoin helps only some patients. A breakthrough seems to be offered by treatment with infliximab (and other biological response modifiers). Surgical resection and reconstruction are necessary for extensive, recalcitrant disease, but local excision is also a good treatment for localized disease.

## Crohn Disease

It can affect any part of the gut and its cutaneous borders from the mouth to the anus. Crohn disease of the penis is rare. Metastatic cutaneous ulceration of the penile shaft, multiple scrotal urinary fistulae and destruction of the proximal urethra have been reported.

## Pemphigus

Pemphigus is a group of rare immunobullous disorders where loss of epidermal cohesion causes blistering and erosion of mucocutaneous sites. Therefore, the penis is often involved but not usually in isolation. Diagnosis is by biopsy and immunofluorescence studies. Treatment requires high-dose systemic corticosteroids and often other immunosuppressant medication.

## Ecthyma Gangrenosum

Ecthyma gangrenosum is usually due to *Pseudomonas* septicemia. A red macule rapidly progressing to a blue bulla, rupturing to form a necrotic ulcer with a central erythematous halo; or painful, tense grouped vesicles, which rapidly become necrotic and form ulcers with black necrotic eschars are the clinical characteristics of ecthyma gangrenosum. It occurs in immunosuppressed patients including children and has a predilection for the extremities and anogenital regions. It may affect the penis in isolation leading to gangrene.<sup>36</sup> The prognosis is generally poor. Patients with hematological malignancy may develop the disease without

**Table 60.8:** Causes of Penile Necrosis<sup>1,2</sup>

Bacterial
Fusospiillary infections
Hemolytic streptococci
Tuberculosis
Syphilis
Ecthyma gangrenosum
Post-operative wound infections
Viral
Herpes simplex
Varicella (in infants)
Drugs
Foscarnet
Quaternary ammonium products (decamethylene bis)
Warfarin
Systemic diseases
Uremic (CRF) secondary hyperparathyroidism
Diabetes mellitus and end-stage renal disease
Diabetes mellitus and small vessel disease
Thrombocytopenia
Polycythemia
Priapism
Tourniquet syndrome
Penile thrombosis
Intravenous drug abusers (heroin addicts)
Fournier gangrene
Decubitus ulcers
Vasculitis
Spider bite
Pyoderma gangrenosum
Wegener granulomatosis
Ecthyma gangrenosum
Calciophylaxis
Leukemia
Cryotherapy

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evidence of *Pseudomonas* septicemia, and in these cases the prognosis is better. The important causes of penile necrosis are given in Table 60.8.

## Pyoderma Gangrenosum

There are a handful of reports of pyoderma gangrenosum involving the penis in adults.<sup>37</sup> It has also occurred on the scrotum. One of the cases was associated with ulcerative colitis and another with chronic lymphocytic leukemia, but the others occurred without any associated disease. Pyoderma gangrenosum is a diagnosis made when other causes of purulent ulceration such

as neoplasia, and artifact have been excluded. It may occur as a Köebner phenomenon to local trauma such as urological surgery. Aggressive therapeutic measures are often required including high-dose oral corticosteroids, intravenous methylprednisolone oral cyclosporine or cyclophosphamide. Minocycline and thalidomide may be beneficial in pyoderma gangrenosum unresponsive to corticosteroids and when associated with Behçet disease. Mycophenolate mofetil and infliximab show promise.

### Herpes Zoster

Sacral and penile herpes zoster is relatively rare, but can be associated with severe morbidity due to nocturia, dysuria, hesitancy, acute urinary retention, constipation, and fecal retention. Painful, grouped crusting vesiculopustular lesions may be found on the buttock, in the perineum, on the scrotum and penis (Fig. 60.25), in the groins, and on the upper thigh. Hospitalization, urological assessment, observation, catheterization, sigmoidoscopy, and possibly, assisted fecal extraction are indicated. Treatment should be with intravenous acyclovir.

### Fournier Gangrene

In 1883, Fournier, a Parisian dermatologist, described five cases of spontaneous genital gangrene and ulceration. Since then several hundred cases have been reported and predisposing factors, clostridial and non-clostridial causative microorganisms have been identified.<sup>1,2,38</sup> Patients present with systemic upset, painful erythematous swelling of the genital, perianal or lower abdominal skin, and some may have urinary retention. An “ominous” black spot may appear on the scrotum. Rapidly, necrosis of skin and

deeper tissues supervenes and death ensues. The mortality may be higher than 50% unless diagnosis is prompt and radical management instituted. There is gross systemic toxicity, and its clinical picture overlaps with necrotizing fasciitis and Meleney gangrene. Risk factors include colorectal disease, diabetes mellitus, alcoholism, anogenital infection, chemotherapy, debilitation, granulocytopenia, HIV, post-instrumentation, post-operative (urological—including vasectomy and colorectal), heroin addiction, trauma, and unusual sexual practices. The process probably begins with appendageal or urethral polybacterial infection, followed by a necrotizing vasculitis affecting skin, subcutis, fascia, and muscle. Radiological studies may show soft tissue gas. The differential diagnosis of Fournier disease includes herpes simplex, streptococcal or staphylococcal cellulitis, streptococcal necrotizing fasciitis, gonococcal balanitis, ecthyma gangrenosum, allergic vasculitis, polyarteritis nodosa, necrolytic migratory erythema, vascular occlusion syndromes, and warfarin-induced necrosis. If the clinical diagnosis of Fournier gangrene is entertained then drastic emergency management is required. Surgical, microbiological, and intensivist assistance are required. Radical surgical debridement of all affected tissue is undertaken and broad spectrum systemic antibiotic therapy initiated. If the patient survives then plastic surgical repair is undertaken. In adults, the mortality is around 25% and is highest in disease of anorectal rather than urogenital origin.

### Tuberculosis

Penile tuberculosis is extremely rare. Primary penile ulceration<sup>39</sup> with or without inguinal lymphadenopathy may occur due to sexual infection or secondary to tuberculosis elsewhere, for example the gastrointestinal system and lung. Not uncommonly, small, punched out ulcerations of papulonecrotic tuberculide occur on the glans penis, and this may be the only site involved (Fig. 60.26).<sup>40,41</sup> Diagnosis is made on the basis of culture and histopathology. Pyoderma gangrenosum, Crohn disease, hidradenitis, neoplasia, artefact,



**Fig. 60.25:** Herpes zoster of shaft of the penis.



**Fig. 60.26:** Papulo-necrotic tuberculide on the glans penis. The lesions on patient's finger are common warts and are unrelated to genital lesions.

sexually transmitted diseases, amoebiasis, and deep mycoses appear in the differential diagnosis. Treatment is by appropriate combination chemotherapy.

## Leishmaniasis

Cutaneous leishmaniasis has been reported on the genitalia.<sup>42</sup> As at other sites, painless papules or pustules progress to chronic ulceration without regional lymphadenopathy. The disease is due to one of several protozoal organisms and is endemic in the Middle East, Asia, and South America. Diagnosis depends on biopsy and identification of Leishman–Donovan bodies. Some lesions may heal spontaneously, but with scarring. Treatment is with the antimonial drug, sodium stibogluconate intravenously.

## Amoebiasis

Cases of amoebiasis presenting as balanitis have been described. Painful swelling and ulceration are the principal clinical features, but frequency, dysuria, and retention may be complications. Most case reports have come from tropical countries, particularly Papua New Guinea. Contamination from an amoebic bowel infection is thought to be the route of infection either by self-inoculation, or by heterosexual intercourse where the female partner has amoebic vaginitis, or by sodomy, which seems the most likely mechanism in Papua New Guinea. Diagnosis is by demonstration of the *Entamoeba histolytica* trophozoites in the mucopurulent discharge or in a biopsy. Treatment is with debridement and oral metronidazole. Sometimes circumcision may be necessary preferably after the diagnosis has been made and antiamoebic therapy initiated.

## Palpable Lesions/Tumors

Inflamed as well as neoplastic tissue can present as palpable lesions (Table 60.9).<sup>1,2</sup>

### Keloid

It has been stated that the skin of the penis never forms keloid, but it has been reported very rarely following circumcision, other surgical procedures, trauma, and burns. Chronic edema resembling keloid on the dorsum of the penis has been reported to complicate the use of a condom catheter for neurogenic bladder.

### Sarcoid

Sarcoid is rare on the genitals but sarcoidosis should be in the differential diagnosis of papules and nodules affecting the penis and scrotum.<sup>43</sup>

## Granuloma Annulare

A few cases of granuloma annulare affecting the penis have been reported. In its localized form, it usually affects the hands and feet perhaps associated with trauma; in its generalized form, it may be associated with diabetes mellitus. Erythematous smooth, round and linear nodules are described.<sup>44</sup>

**Table 60.9:** Palpable Lesions<sup>1,2</sup>

Reddish/flesh-colored papule	Pigmented papules
<b>Non-infective conditions</b>	Skin tags
Lichen nitidus	Basal cell papilloma
Angiofibroma (pearly penile papules)	Melanocytic naevus
Fordyce glands (ectopic sebaceous glands)	Viral wart
Penile and scrotal calcinosis	Dermatofibroma
Angiokeratoma corporis diffusum	Naevus comedonicus
Skin tags	Langerhans cell histiocytosis
Basal cell papilloma	Malignant melanoma
Sebaceous hyperplasia	<b>Cysts and nodules</b>
Neurofibroma	Basal cell papilloma
Leiomyoma	Keloid/scar
Epidermoid cysts	Sarcoidosis
Mucoid cysts (congenital)	Crohn disease
Acanthosis nigricans	Hidradenitis suppurativa
Langerhans cell histiocytosis	Lymphangioma circumscriptum
Malignant melanoma	Non-venereal sclerosing lymphangitis
Sarcoidosis	Epidermoid cyst
Granuloma annulare	Median raphe cysts
Lichen planus	Mucoid cysts
Angiomas	Scabies
Angiokeratoma of Fordyce	Pilar cyst
Dermatofibroma	Penile and scrotal calcinosis
<b>Infective conditions</b>	Foreign body
Tuberculide (lichen scrofulosorum, papulonecrotic tuberculide)	Lipogranuloma
Kaposi sarcoma	Silicon granuloma
Early chancre of primary syphilis	Appendageal tumors
Primary granuloma inguinale (donovanosis)	Neurofibromas
Primary lymphogranuloma venereum	Giant cell fibroblastoma
Schistosomiasis	Langerhans cell histiocytosis
Inflamed mollusc	Basal cell carcinoma
Inflamed viral warts	Penile horn
	Squamous cell carcinoma
	Malignant melanoma
	Kaposi sarcoma
	Penile metastases
	Chronic lymphocytic leukemia

(Reproduced from: Bunker CB. *Male Anogenital Skin Disease*. London: Saunders, 2004).

## Schistosomiasis

Perineal granulomatous lesions are a rare manifestation of schistosomiasis (*Schistosoma haematobium*), which is endemic in many parts of the world and contracted by swimming in water containing infected fresh-water snails. It may present with skin symptoms and signs at the time of infection or later with hematuria. Rarely, genital skin lesions may lead to the diagnosis. The papules and nodules may be skin colored, pink or brown, scattered or grouped, affecting the penis, scrotum, and vulva. They can spread onto the perineum and around the anus and may develop into soft warty vegetating lesions, but remain relatively asymptomatic. Ulceration is rare. Diagnosis is by biopsy which shows eosinophilic infiltration (there may be a blood eosinophilia) or frank giant cell granuloma formation around viable and calcified *S. haematobium* ova with a characteristic terminal spine. Other granulomatous conditions, especially tuberculosis, may be suspected. Ova may be recovered from urine or stool. Treatment of choice for *S. haematobium* is praziquantel.



## Amyloid

The non-tender, smooth, yellowish, waxy, occasionally hemorrhagic papules that constitute the most common cutaneous lesion of primary systemic amyloidosis have predilection for the anogenital region, as well as the face. Amyloidosis focalized to the penis is very rare (six cases).<sup>45,46</sup> Primary amyloid of the urethra is very rare but accurate diagnosis is essential as it presents like penile carcinoma with dysuria, bloody discharge, and tender induration of the penis.

## Syringoma

Syringoma is a common benign tumor of eccrine sweat glands usually occurring as multiple symmetrical flesh-colored papules around the eyelids. Rarely, there may be a more widespread distribution. Some cases of multiple syringoma focalized to the penis have been described.<sup>47</sup>

## Non-venereal Sclerosing Lymphangitis/ Penile Venereal edema

Non-venereal sclerosing lymphangitis/penile venereal edema/Mondor phlebitis/localized penile lymphedema/penile lymphocele has become increasingly recognized in recent times and probably went unrecorded previously.<sup>1,2,48–50</sup> Patients present with a serpiginous mass in the coronal sulcus spreading sometimes on to the dorsal penis (Fig. 60.27). The lesion may appear for the first time or become tender and enlarge after prolonged or frequent sexual intercourse. The problem usually resolves spontaneously or may rarely require surgical excision.



Fig. 60.27: Non-venereal sclerosing lymphangitis.

## Dermatofibroma

Dermatofibroma or fibrous histiocytoma is a very common benign lesion of skin, but curiously, rather rarely, if ever, found in the anogenital area. It is thought to represent aberrant healing following an insect bite. One penile case appears in the literature in an 8-year-old boy.<sup>51</sup>

## Epidermoid and Pilar Cysts

These lesions are probably much more common than the literature attests. Giant or unusual lesions only attract attention.<sup>52</sup>

## Scrotal Calcinosis

Scrotal calcinosis is a relatively common, benign idiopathic disorder presenting as rock hard, smooth white papules or nodules on the scrotum (Fig. 60.28). It is much rarer on the vulva. Occasionally, they may become secondarily inflamed or infected following trauma. In endemic areas of onchocerciasis, like West Africa, calcified scrotal cysts may be due to the living or dead nematodes of *Onchocerca volvulus*. Patients usually have evidence of the disease elsewhere.<sup>53</sup> Treatment is surgical but recurrence is frequent.

## Verruciform Xanthoma

Verruciform xanthoma is a rare entity and presents as a painless, yellow-brown or red, verrucous, sessile or papillary plaque. It has a predilection for the oral mucosa but cases affecting the anogenital region have been described.<sup>54</sup> Treatment is by surgical excision.

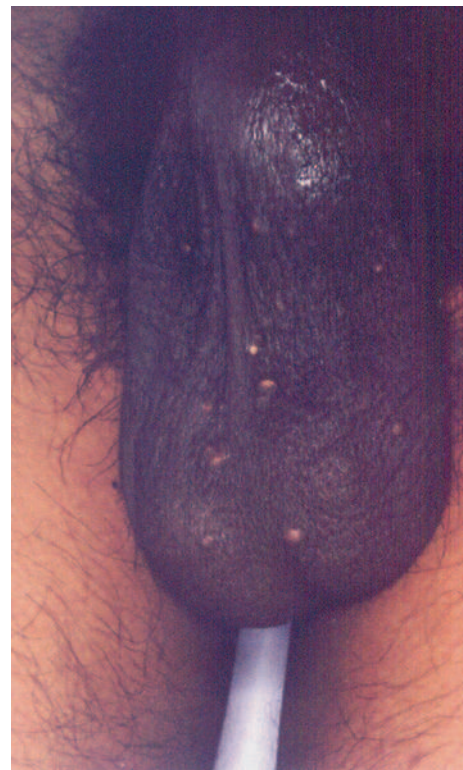


Fig. 60.28: Nodules of scrotal calcinosis.

## Langerhans Cell Histiocytosis

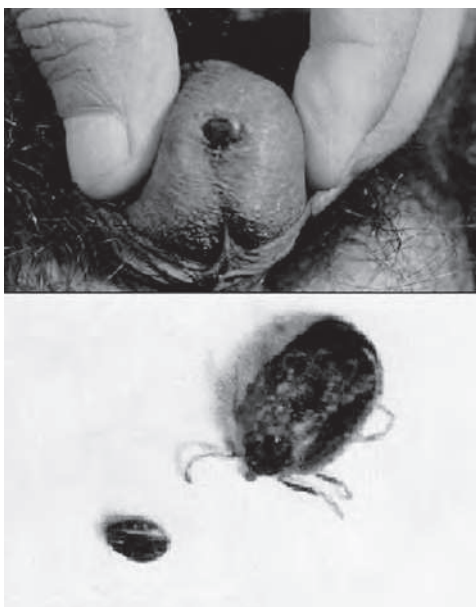
Solitary to multiple, pruritic, yellowish-red brown papules or nodules, with central foci of ulceration, sometimes in clusters, with crust or scale, involving the perineum or inguinal regions but also other skin folds and non-intertriginous sites in a child, or occasionally an adult should arouse the suspicion of Langerhans cell histiocytosis.<sup>55,56</sup> Primary penile ulceration has been reported as a presentation.<sup>55</sup> Full assessment should be undertaken to exclude systemic disease, which manifests as exophthalmos, lymphadenopathy, hepatosplenomegaly, and polyuria.

## Foreign Body

Oil, silicon, plastic or glass beads, small smooth stones may be introduced into the skin of the penis and cause clinical and radiographic confusion. These can elicit a paraffinoma, silicone granuloma or sclerosing lipogranuloma.<sup>1,2</sup> In the Philippines, the practice is called “bullectus,” in Sumatra “persimbraon” and in Korea “chagan ball.” In Thailand, it is called “muksha,” or “tanchu” after a Japanese hair pomade whose glass container is melted down and fashioned into glass balls that are then inserted subcutaneously in the penile shaft. The insertion of real pearls has been reported—papular pearly penile pearls. These practices are believed to have started in the far east after the second world war. Rarely, an insect may enter the urethra and be visible through the external urethral meatus (Fig. 60.29).

## Penile Horn

Cutaneous horns (Fig. 60.30) are a type of verrucous lesion marked by excessive and increasing keratosis.<sup>47</sup> Only a few cases of penile



**Fig. 60.29:** Insect with its egg in the penile urethra. Courtesy: Dinesh Govil, Jhansi, India.



**Fig. 60.30:** Penile cutaneous horn with underlying squamous cell carcinoma. Courtesy: Amrinder J Kanwar, Chandigarh, India.

horn have been reported. The hyperkeratosis of the cutaneous horn may eventuate from numerous dermatological lesions including burns, naevi, angiomas, Bowen disease, condyloma acuminata, actinic keratoses, seborrheic keratoses/basal cell papillomas, basal cell carcinoma, verrucous carcinoma, and squamous carcinoma. Chronic inflammation and recent circumcision for long-standing phimosis are important predisposing factors. The lesion is premalignant or, in one-third of cases, malignant at presentation with squamous cell carcinoma being the underlying pathology. Treatment should be by adequate excision and follow-up because recurrence may occur.

## Basal Cell Carcinoma

Basal cell carcinoma is a locally invasive neoplasm of the pilosebaceous apparatus. Although the most common type of skin cancer, it is rare in the anogenital area because sun exposure is more important as an etiological factor than biological age. It presents as an indolent nodule or ulcer with a pearly edge: occasionally it is pigmented or flat and morphoeic. Basal cell carcinoma very very rarely and metastasizes multiple erosive scrotal basal cell carcinomas and are associated with this risk. It can be a straight-forward clinical diagnosis elsewhere on the body, but less easy around the genitalia where it may not be suspected because of its rarity.<sup>57</sup> Surgical excision is the treatment of choice.

## Porokeratosis

Genital porokeratosis of Mibelli is rare.<sup>58</sup> Annular raised, double-rimmed lesions have been found in the natal cleft and on the penis and scrotum. They may be misdiagnosed clinically as granuloma annulare or lichen planus but biopsy through the edge shows the characteristic coronoid lamella histologically.

## Pseudoepitheliomatous, Micaceous, and Keratotic Balanitis (PEMKB)

Pseudoepitheliomatous micaceous and keratotic balanitis is a very rare penile condition.<sup>1,2,15</sup> It presents as thick, scaly, micaceous



patches on the glans penis from which a verrucous or erosive tumor may emerge. It occurs in older men who have not been circumcised. It has been misdiagnosed as Reiter disease. PEMKB is probably a form of lichen sclerosus-related locally invasive verrucous carcinoma.

Metastases have not been reported except in association with penile cutaneous horns. Treatment can pose a difficult problem with recurrence and chronicity being common. Topical 5-fluorouracil (5-FU), radiotherapy, and surgery have all been suggested.

### Penile Carcinoma in Situ (PCIS)

Erythroplasia of Queyrat (EQ) and Bowen disease (BD) of the penis (Fig. 60.31) describe carcinoma *in situ* of the penis (PCIS).<sup>1,2,59–61</sup> They are synonymous in this respect, although BD is used to refer to squamous cell carcinoma *in situ* at other cutaneous sites. EQ should be used as a term for red, shiny patches or plaques of the mucosal sites, glans and prepuce of the uncircumcised, and BD for red scaly patches and plaques of the keratinized sites. Bowenoid papulosis (BP) is an analogous, but distinct, entity and presents as multiple small flat topped, often pigmented pink or skin colored papules coalescing to form plaques (Fig. 60.32). It usually occurs in young, sexually active circumcised men, primarily

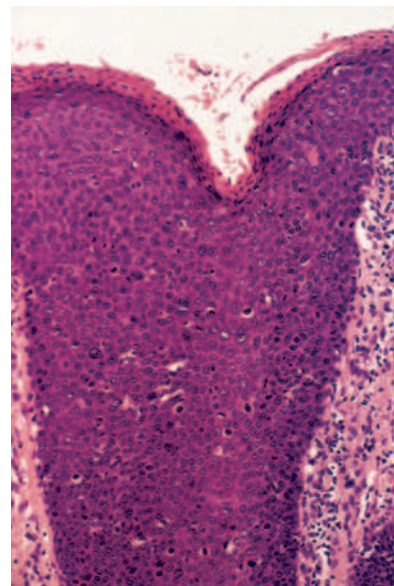
on the penile shaft but can also occur on the glans, prepuce, and frenulum. BP is associated with multiple HPV subtypes, including benign subtypes (6 or 11) and the oncogenic subtypes 16, 18 and 33. Penile intraepithelial neoplasia (PIN—corresponding to CIN, VIN, and AIN) is an increasingly encountered term, and is used here as a clinical umbrella, but there is as yet no formal consensus on clinicopathological classification and clinical utility.<sup>62</sup> All describe disorders of the penis in uncircumcised, predominantly Caucasian men. Circumcised patients with PCIS have been recorded. Some patients may be quite young. The non-specificity of the clinical appearances makes for an important differential diagnosis which includes inflammatory disorders, such as psoriasis, lichen sclerosus, erosive lichen planus and Zoon balanitis, and cancerous conditions such as Kaposi sarcoma. BP may be mistaken for viral warts, lichen planus, basal cell papilloma, naevi, mollusca, and condylomata lata. A biopsy is indicated in most instances. The histology is of squamous carcinoma *in situ*. (Fig. 60.33) Treatment depends on many factors. It should begin with circumcision. At a stroke, this removes a major risk factor for cancer, provides extensive tissue for histology and an opportunity under anesthesia to examine the whole organ and obtain further biopsies. 5-fluorouracil as a 5% cream is a conventional option for the treatment of BD/EQ/BP. There have been no clinical trials but there have also been no reports of significant local or systemic side effects that save circumlesional irritation. A useful clinical regimen is to use cyclical 5-FU and topical corticosteroid treatment. Other treatments include cryosurgery, curettage and



**Fig. 60.31:** Bowen disease on the background of Lichen Sclerosus.



**Fig. 60.32:** Bowenoid papulosis



**Fig. 60.33:** Intraepithelial neoplasia. Full thickness dysplasia with moderate to marked pleomorphism of the nuclei, increased numbers of mitotic figures which are right in the epidermis, the changes extend down and around a follicle: Bowenoid dysplasia of a high grade. Courtesy: Nick Francis, London, UK. Reproduced with permission from: Male anogenital skin diseases, Ref.2.



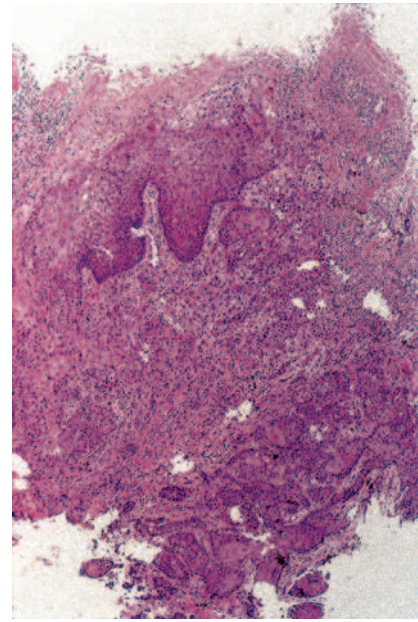
electrocautery, excisional surgery, micrographic surgery, laser, and topical or systemic photodynamic therapy. Patients and their sexual partners presenting with these conditions should be counselled and screened for HPV and other sexually transmitted diseases including HIV infection. Smoking should be discouraged. Follow-up should be long term.

## Squamous Cell Carcinoma

Itch, irritation, pain, bleeding, discharge, ulceration or the discovery of a lump (Fig. 60.34) reveal squamous cell carcinoma.<sup>1,2,62</sup> There is usually a long history of problems with the penis and foreskin amounting to dysuria, dyspareunia, balanoposthitis or phimosis. Irregular nodular and ulcerative morphology is encountered. Background BD/EQ/BP, lichen sclerosus or even lichen planus may be detected. Phimosis should be regarded as a sinister situation and impedes complete inspection and palpation of the glans and coronal sulcus. The presence or absence of inguinal lymphadenopathy should be ascertained, although in penile cancer only 50% of enlarged glands will be found to contain tumor. It is important to establish the presence of other disease states, particularly sexually transmitted diseases and immunocompromise. The differential diagnosis includes the manifestations of PCIS and other erosive or ulcerative sexually transmitted disease, basal cell carcinoma, Kaposi sarcoma, Fournier gangrene, pyoderma gangrenosum, and artefact. Genitourinary and urological assessment and biopsy are mandatory. In all patients with suspected squamous cell carcinoma, topical imiquimod histologic confirmation is necessary (Fig. 60.35). Adequate surgical excision is required. This may need to be radical (i.e., penile amputation) depending on location and extent.



**Fig. 60.34:** Squamous cell carcinoma of the penis.



**Fig. 60.35:** Invasive squamous carcinoma. The surface shows hyperkeratosis and acanthosis. Deep to that there is chronic inflammation and extensive infiltration of the underlying tissue by islands of moderately differentiated squamous carcinoma. Reproduced with permission from: male anogenital skin diseases, Ref.2.

Lymphatic or hematogenous dissemination requires individualized multidisciplinary management. The prognosis is poor. Recurrence and progressive malignant transformation does occur. The options of Mohs' micrographic surgery, laser destruction, and adjuvant interferon alpha 2b should be considered. The precise etiology of the types of PIN, verrucous carcinoma, and frank invasive squamous cell carcinoma of the penis is unknown. The natural history of EQ/BD would be consistent with a local carcinogenic influence in uncircumcised men. Smegma has been proposed as that factor with additional contributions from poor hygiene, trauma, friction, heat, maceration, and inflammation. Quantifying the malignant potential of BD/EQ/BP/PCIS is not easy, but they are acknowledged risks for penile cancer. The presence of a foreskin confers cancer risk. Circumcision appears to protect against penile carcinoma unless the circumcision was performed for penile disease. But cases of malignancy in those circumcised at birth have occurred. Carcinoma of the penis accounts for less than 1% of deaths from cancer in the USA but constitutes 10–20% of tumors seen in males in either underdeveloped countries or in areas where early circumcision is not routinely practised. Phimosis and balanitis are known risk factors for penile cancer. Poor personal and sexual hygiene and phimosis may lead to the retention of smegma and balanitis. Also it has not been widely appreciated that phimosis is a physical sign and not a diagnosis. There may be more in the carcinogenic propensity of phimosis than simply physical retention of smegma. Lichen sclerosus, a common cause of phimosis in men, is a premalignant

condition predisposing to penile carcinoma. Chronic erosive and hypertrophic lichen planus are also premalignant conditions and can cause phimosis. Smoking is a risk factor independent of phimosis for penile carcinoma and is also a recognized risk factor for cervical cancer. Smoking may cause squamoepithelial cancer not only in parts of the body in contact with smoke, but also at distant sites by dissemination of carcinogens in the circulation or in secretions. Penis cancer has been reported to complicate renal transplantation, PUVA (psoralen ultraviolet A), photochemotherapy, and possibly other treatments for psoriasis. The risk of penis cancer is five to six fold increased in HIV infection. Although penile carcinoma is associated with multiple sexual partners and previous sexually transmitted disease, the epidemiological features are not those characteristic of a sexually transmitted disease—unlike carcinoma of the cervix and to a lesser extent anal carcinoma, where the evidence is for STD with HPV as the etiological agent. Yet penile cancer puts wives and partners at risk of cervical cancer. There is a high prevalence in sexual partners of women with cervical intraepithelial neoplasia (CIN), and PCIS can be found in men being screened for infection. HPV may be found in the lesions of EQ/BD/BP (Types 8, 16, 18, 31, 42) and in 15–80% of penile cancers (Types 16, 18, 31, 33, 35), but there are exceptions. It has been suggested that EQ may be defined by co-infection with HPV type 8 and other carcinogenic HPV types.<sup>63</sup>

### Verrucous Carcinoma/Buschke Löwenstein Tumor (BLT)/Giant Condyloma

Verrucous carcinoma<sup>1,2</sup> is a rare, low-grade, well-differentiated squamous carcinoma. It is a dramatic clinical lesion, often polypoid or cauliflower like. Although, locally deeply invasive, it is well-demarcated from surrounding tissue and probably does not metastasize. Suspected verrucous carcinoma demands a deep surgical biopsy. Frank squamous carcinoma and foci of invasive squamous carcinoma have been reported in some cases of anogenital verrucous carcinoma. A specific etiology for verrucous carcinoma/BLT has not been identified, but an apparent origin from common genital warts is thought likely. BLT is firmly associated with low risk HPV types 6 and/or 11. A relationship with lichen sclerosus has also been observed.

### Malignant Melanoma

Malignant melanoma of the penis is a very rare condition. There are less than 100 cases in the literature.<sup>1,2,64</sup> It is estimated to account for 1–1.5% of all malignancies of the penis and less than 0.15% of all melanomas. Melanoma is even rarer on the scrotum with only four cases appearing in the literature. Vulval melanoma is commoner. Melanoma presents as pigmented macules or as a pigmented or amelanotic papule or nodule (possibly developing from a lentiginous area or pre-existing dysplastic naevus), which may ulcerate or bleed. Patients are usually middle aged or older, although it has been reported in a boy. It is exceedingly rare in Asians and has not been reported

in blacks. Melanoma of the urethra has been described.<sup>65</sup> Sixty to seventy percent of the lesions occur on the glans. There may be a family history of melanoma and other atypical or “dysplastic” naevi on examination. Forty to fifty per cent of patients have lymphatic or other metastatic dissemination at the time of presentation. Treatment is by primary excision. Subsequent management depends on the Breslow thickness of the lesion and complete clinical staging. Radical surgery and chemotherapy may be needed, but the prognosis is poor for all melanomas that have already metastasized.

### Extramammary Paget Disease

Extramammary Paget disease presents as an irritating, itchy, burning, red scaly patch, patches or plaques. Paget disease can be found anywhere around the anogenital area, including the glans penis and may be multicentric. It is frequently misdiagnosed as an inflammatory dermatosis, such as psoriasis. A biopsy is mandatory. The disease behaves indolently, spreading by local extension and metastasis.<sup>1,2</sup> Mammary Paget disease is an epidermal manifestation of an underlying breast adenocarcinoma. Extramammary Paget disease is found in areas rich in apocrine sweat glands, such as the axillae and anogenital region. It can be associated with an underlying malignancy. While considered to represent a form of carcinoma *in situ*, it may, itself, become invasive and there may be subjacent carcinoma, for example in periurethral glands or more distant cancer of the prostate or bladder. Co-existent genital and extragenital Paget disease is extremely rare. Paget disease has been treated with cryotherapy and topical 5—fluorouracil. Widespread excisional surgery like Mohs’ and plastic repair (if needed) is probably the treatment of choice. Topical imiquimod shows promise in obviating or limiting the extent of surgery.<sup>61</sup> Radiotherapy is regarded as ineffective. Photodynamic therapy may be useful.

### Mycosis Fungoides

Mycosis fungoides is a cutaneous T-cell lymphoma. It can be difficult to diagnose clinically and histologically and runs a long, indolent, and variable course. Fixed, red, scaly eczematoid or psoriasiform patches and plaques are the early signs. These may be easily diagnosed as due to one or other benign inflammatory dermatosis and respond partially and intermittently to topical corticosteroid treatment. Localized anogenital disease has been described.<sup>66,67</sup>

### Kaposi Sarcoma

Genital KS is an important entity.<sup>1,2,68</sup> Solitary KS of the penis was recognized, if rarely, before the HIV epidemic. In patients with HIV infection, KS can occur as a dull red patch or plaque on the glans penis or preputial sac, as well as one of its more classical manifestations, namely purple, slightly scaly patches or plaques, nodules, or ulcerative lesions. An engorged, “hypervascular” presentation has been reported, as has been phimosis. KS is common in homosexuality associated

**Table 60.10:** Treatment Options for Kaposi Sarcoma

Local	Systemic
Cryotherapy	Aggressive chemotherapy
Radiotherapy	Liposomal doxorubicin
Intralesional, e.g., TNF $\alpha$ , IFN $\gamma$	Isotretinoin
Vinca alkaloids	
Surgery	
Cosmetic camouflage	

HIV, but less so in intravenous drug abusers and hemophiliacs. Classical KS occurs in elderly male central Europeans, Italians or Jews, and is solitary and acral. Endemic KS occurs in black Africans and is florid and aggressive. A third group of KS occurs in patients with iatrogenic immunosuppression. AIDS-related KS is multicentric and often involves the face, oral mucosa, palate, and genitalia. The characteristic lesion is a purple nodule, which may ulcerate. The differential diagnosis includes naevi, angioma, angiokeratoma, and histiocytoma, but cryptococcosis, histoplasmosis, leishmaniasis, pneumocystis, and dermatophytosis may also mimic and/or complicate KS. KS masquerading as pyogenic granuloma has become a well-recognized clinical presentation, as has bacillary angiomatosis masquerading as KS. KS is now known to be due to human herpes virus 8. There is no cure for KS but lesions may involute with highly active antiretroviral therapy (HAART). Radiotherapy, local and systemic chemotherapy, liposomal doxorubicin have their places in management (Table 60.10).

## Penile Metastases

Metastases to the penis are rare, but several hundred cases have been reported.<sup>69</sup> They are usually secondary to cancer of the urogenital tract (e.g., bladder or prostate) or gastrointestinal system (e.g., rectum). They may present with pain, swelling, priapism, urinary symptoms, or hematuria. A cutaneous nodule or nodules may be seen or infiltration of the deeper penile structures palpated.

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# Vulvar Dermatoses

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• Andrew T. Goldstein • Nellie Konnikov

# 61

## Introduction

Vulvar dermatoses are the non-neoplastic, non-venereal epithelial disorders of the labia minora, labia majora, and vaginal introitus. Both keratinized skin and mucocutaneous surfaces may be affected. Such dermatoses may begin insidiously, be present for a long time without subjective symptoms, or declare themselves in the form of intractable itch, which may lead to severe discomfort. In addition, they may be a heralding sign to systemic autoimmune disorders or vulvar malignancy. Thus, being able to recognize and treat the vulvar dermatoses is not only vital for comfort but also for the overall health of the patient. This chapter will herald the most prevalent dermatoses affecting external genitalia in women.

## Taking History

Due to the sensitive nature of complaints related to the vulva, practitioners must take time to determine the extent of the disease, otherwise suboptimal treatment may result. The physician should investigate the onset and duration of the problem as well as the specific location, any aggravating or alleviating factors, and the character of the symptoms (itching vs. pain). In particular, one should determine whether the problem is affecting micturition, defecation, or sexual functioning. One should ask about current sexual practices, history of sexually transmitted diseases, and any history of genital surgeries such as labiaplasty. Past medical history, family history, medications, especially any topical preparations or over-the-counter products applied to the vulva, and allergies may be relevant to vulvar problems as well.

## Physical Examination of the Vulva

The examination should be undertaken using proper lighting with the patient placed in the dorsal lithotomy position. One may also want to keep a mirror on hand in case the patient would like to identify areas of concern. A camera may be useful for documenting a baseline physical examination. First, one should examine the external vulva for any growths, erythema, ulcerations, erosions, atrophy, lichenification, or tenderness. Then,

examine the internal vulva, making note of any adhesions and architectural abnormalities, including phimosis of the clitoris and narrowing of the introitus. One may apply a sterile cotton swab to the vestibule of the vulva to determine tenderness. For better view of the vagina, one may utilize a speculum. Culture swabs may also be taken if there is a suspicion of infection at the time of examination.

If the physical examination reveals atypical lesions or abnormal epithelial tissue in the vulva, a biopsy may be undertaken to confirm the diagnosis.

## Differential Diagnosis

For the purposes of this chapter, we will focus on the most common vulvar dermatoses such as papulosquamous and bullous diseases. Primary and secondary skin lesions on genitalia may include patches, papules and plaques, vesicles, erosions, and scarring. While evaluating the patient with vulvar problems, the clinician should generate a broad differential diagnosis based on the morphology of presenting lesions (Table 61.1). Within each of those categories, the clinician ought to consider a wider list of inflammatory processes, infections, and malignancies. While some infections, such as herpes simplex are more common, relatively rare infections may also been seen, particularly in the HIV positive population, including histoplasmosis, cryptococcus, coccidiomycosis, blastomycosis, molluscum contagiosum, and cutaneous tuberculosis. The HIV positive patients are also more likely to show signs of premalignant or malignant conditions such as florid condyloma accuminata, squamous cell carcinoma, and Kaposi sarcoma. The clinician will then use objective data gathered from physical examination, laboratory workup, and biopsy to settle on a diagnosis.

## Lichen Sclerosus

Lichen sclerosus (LS) is a chronic inflammatory and potentially scarring disorder of the vulva and the perianal region and sometimes the other extragenital sites. In the male counterpart, penile involvement is quite common. Originally described by Hallopeau

**Table 61.1:** Nonvenereal Vulvar Dermatoses

Papules	Inflammatory dermatoses
Angiokeratoma	Lichen sclerosus
Acrochordon	Lichen planus
Fox–Fordyce disease	Psoriasis
Seborrheic keratosis	Lichen simplex chronicus
Vestibular papillomatosis	Discoid lupus erythematosus
Cherry angioma	Tinea
Folliculitis	Erythrasma
Syringomas	Seborrheic dermatitis
Hemangioma	Allergic contact dermatitis
	Irritant contact dermatitis
	Radiodermatitis
Vulvar lesions in systemic disease	Pigmentary alterations
Inflammatory bowel disease	Vitiligo
Systemic lupus erythematosus	Lentigenes (including
Acrodermatitis enteropathica	genodermatoses with
Glucagonoma syndrome (Necrolytic migratory erythema)	genital mucosal lentigenes such as Laugier–Hunziker syndrome)
Ulcers and erosive diseases	Cysts/nodules
Erosive lichen planus	Epidermoid cyst
Lichen sclerosus	Bartholin cyst
Pemphigus vulgaris	Mucinous cyst
Cicatricial pemphigoid	Hidradenomas
Hailey–Hailey disease	Hidradenitis suppurativa
Epidermolysis bullosa aquisita	Endometriosis
Linear IgA disease	
Toxic epidermal necrolysis	
Stevens–Johnson syndrome (Erythema multiforme major)	
Fixed drug eruption	
Herpes zoster	
Herpes simplex	
Candidiasis	
Impetigo (Staphylococcal/ Streptococcal)	
Pyoderma gangrenosum	
Aphthous ulcer(s)	
Behçet disease	
Ulcerated tumors (Squamous cell carcinoma and other tumors)	
Extramammary Paget disease	
Premalignant lesions	Malignant lesions
Vulvar intraepithelial neoplasia	Squamous cell carcinoma
Condyloma acuminata	Basal cell carcinoma
Paget disease	Adenocarcinoma
Bowen disease	Melanoma
Bowenoid papulosis	Metastatic tumors
Lichen sclerosus	Sarcomas
Zoon vulvitis	

in 1889, the vulvar form primarily affects postmenopausal women and young children, appearing during times of low hormonal output.<sup>1</sup> One study showed an incidence of vulvar LS in 1.7% of patients presenting to a general gynecology practice.<sup>2</sup> The disease may be associated with systemic autoimmune disorders as well as vulvar malignancy with disease progression. A study of 190 women with LS showed 28% to have one or more autoimmune disorders, over half of them with thyroid disease; other prevalent disorders included alopecia areata, pernicious anemia, and morphea.<sup>3</sup> A retrospective review of 202 patients with LS showed that

17% had extragenital psoriasis on examination, compared with 2–3% in the general population.<sup>4</sup> Etiology is unknown, but basic research suggests that genetic predisposition to autoimmunity, chronic infections, mechanical forces of friction or rubbing, and specific autoimmunity to elements of the extracellular matrix and basement membrane zone may all play a role.<sup>5–7</sup>

## CLINICAL PRESENTATION

Patients generally present with complaints of pruritus, soreness, or dyspareunia, although they may also remain asymptomatic. Young females with the disease may mention urinary or bowel symptoms. Clinicians should also investigate a history of thyroid or other autoimmune disorders in the family.

The physical examination classically shows vulvar hypopigmentation and thin, wrinkled and atrophic skin, often in a figure-of-eight distribution around the vulva and the anus. There may be hyperkeratotic as well as eroded areas of the vulva. Fissures and erosions present in the perineal area may be responsible for pain during defecation, and the hesitancy to defecate may lead to symptoms suggestive of constipation.<sup>8</sup> Young girls may also present with an infantile perineal protrusion, a pyramidal soft tissue swelling along the median perineal raphe.<sup>9</sup> Early on in the disease, the vulva may appear whitened and edematous with possible resorption of the labia while later in the disease the labia demonstrate more of a wrinkled “cigarette paper” appearance. (Fig. 61.1)

The thinned skin may also demonstrate ecchymosis, telangiectasias, hemorrhagic blisters, or purpura, the latter of which is more often seen in young girls.<sup>10</sup> External genitalia may exhibit structural changes due to scarring. One may see burying



**Fig. 61.1:** Lichen sclerosus. Courtesy: Andrew Goldstein, MD.

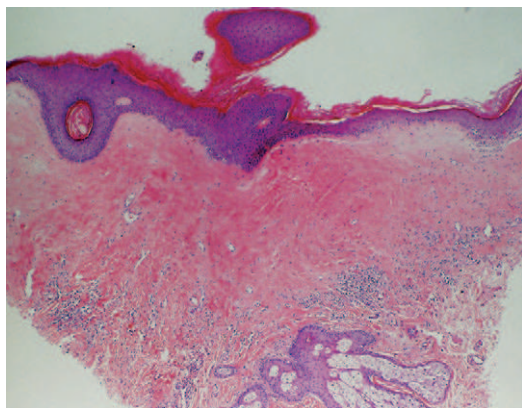


of the clitoris under the clitoral hood, fusion of the labia minora to the labia majora, or more extensive midline fusion. In severe disease, the complete loss of labia minora may result in narrowing of the introitus. These features of the late disease may lead to the clinical diagnosis. If the disease has progressed without medical monitoring, a patient might present with a squamous cell carcinoma arising within the vulvar LS. Extragenital LS is seen in 15–20% of patients with genital LS, particularly in the submammary region, the shoulders, neck, and wrists, presenting as asymptomatic or slightly itching white wrinkled patches of skin showing small pigmented lesions or hyperkeratotic plugs in relation to follicles.

## DIAGNOSIS

Early LS may appear similar to many papulosquamous eruptions or dermatitis; however, more advanced disease may be confused with other scarring disorders, including erosive lichen planus, mucous membrane pemphigoid, and morphea. To rule out these disorders, laboratory and pathologic investigations are often indicated. Given the strong association with autoimmune disorders, one may consider checking hemogram, vitamin B12, TSH, and blood glucose. As eroded vulvar skin may increase the predisposition for infection, bacterial and viral culture may be helpful.<sup>8</sup> A skin biopsy taken from the edge of a lesion will establish the diagnosis definitively and is particularly indicated if any growths noted within the vulvar LS. The histology classically demonstrates compact orthokeratosis, follicular plugging (nonmucosal sites), a thinned epidermis, vacuolization of the basal layer, and hyalinization of the papillary dermis. A thick lichenoid lymphocytic infiltrate may be seen. Squamous hyperplasia is not uncommon (Fig. 61.2).

If there is erosion, direct immunofluorescence (DIF) would help to differentiate LS from mucous membrane pemphigoid. The DIF will be negative in LS. Biopsy is less practical in very young females as it may require general anesthesia.<sup>11</sup>



**Fig. 61.2:** Histopathology of lichen sclerosus. *Courtesy: Andrew Goldstein, MD. Fig. 61.1: Lichen sclerosus. Courtesy: Andrew Goldstein, MD*

## TREATMENT

Disease control is a key to remission and prevention of malignant transformation in LS. Ultrapotent topical corticosteroids are the standard treatment for vulvar LS. Efficacy in controlled trials has been demonstrated for clobetasol propionate 0.05% ointment. Initial therapy with clobetasol ointment 0.05% includes once daily application for 3 months, followed by once to twice weekly application as needed for maintenance.<sup>8</sup> Often patients have improvement in symptoms within weeks, including decrease in erythema if scarring has not yet occurred.<sup>10</sup> The risks of chronic clobetasol use include skin thinning and telangiectasia and must be weighed against the benefits of prevention of scarring, especially in small children. A retrospective chart review of 129 women with LS demonstrated that after induction of remission with super potent topical corticosteroid, 98% of the patients were maintained on remission using low-to-moderate potency topical corticosteroids titrated to treat symptoms.<sup>12</sup> Second-line treatments include the topical calcineurin inhibitors, which have shown efficacy and safety in a clinical trial, with 43% of patients achieving disease clearance after 16 weeks of twice daily treatment with tacrolimus ointment 0.1%.<sup>13,14</sup>

Surgical correction may be appropriate when LS has caused severe distortion of vulvar architecture.<sup>15</sup> In particular, a Fenton procedure may be performed to alleviate painful splitting of the posterior forchette.<sup>16</sup> Topical testosterone has been used and shown to cause virilization, therefore, is not recommended. One may also recommend use of soap-free cleansers and fragrance-free emollients to reduce any irritation and sensitization of the skin and mucous membranes. If there is an indication, one should treat any concomitant infections in the genital area with appropriate antibiotics and antifungals. Patients should be recommended to use adequate lubrication during sexual intercourse, and in cases of severe associated sexual dysfunction, support groups or sexual counseling may be of benefit.<sup>8</sup> Both patients and clinicians must engage in lifelong monitoring and follow-up for disease progression and potential development of malignancies.

## Lichen Planus

Lichen planus (LP) is an inflammatory, autoimmune vulvar disease which is often part of a more extensive disease of the skin and mucous membranes. While nonmucosal LP is more self-limited condition, vulvar LP is often longer-lasting and affects both keratinized and mucosal surfaces of the genitalia. The disorder was first described in 1867 by Erasmus Wilson.<sup>17</sup> Most patients with vulvar LP are women in the 6<sup>th</sup> decade of life.<sup>5</sup> Genital disease can take four clinical variants: genital disease in the setting of cutaneous disease, hypertrophic disease, erosive disease, and lichen planopilaris. Erosive LP may cause extensive disease of the vulva, the vagina, and the oral mucosa, and was first recognized in 1980s by Pelisse, who coined the name “vulvovaginal-gingival syndrome.” Though the cause of LP is unknown, the accepted theory is that activated T cells begin attacking basal keratinocytes.<sup>5</sup> Unlike solely cutaneous LP,

erosive vulvar LP has been associated with autoimmune disorders, particularly thyroid disease, as well as antinuclear (25%) and antithyroid (19%) antibodies.<sup>3</sup> In addition, the vulvovaginal-gingival syndrome has been associated with HLA-DQB1\*0201 allele.<sup>18</sup>

## CLINICAL PRESENTATION

Patients with vulvar LP often present vulvar or vaginal discharge, intense pain, itching, burning, dyspareunia, and postcoital bleeding. Patients may demonstrate distress and anxiety over the problem, particularly as it relates to sexual functioning.<sup>2</sup> A cohort of 42 Italian women with histologically confirmed oral LP demonstrated a 57% prevalence rate of vulvar LP.<sup>19</sup> Thus, there is significant disease overlap between different clinical forms of LP.

Similar to cutaneous LP, vulvar disease may present with classic violaceous flat-topped papules and plaques on the labia majora, labia minora, or the mons pubis in a symmetric fashion. Patients with erosive LP usually present with glassy, brightly erythematous erosions associated with Wickham striae noted in the form of peripheral whitening (Fig. 61.3).

In a study of 161 vulvar LP patients, 74% had erosions, 66% had red/purple color, 63% had scarring, and 56% had reticulated lesions.<sup>3</sup> In the hypertrophic disease, hyperkeratotic white plaques are usually limited to the perineum and may resemble squamous cell carcinoma. Erosive LP, often part of the vulvovaginal-gingival syndrome, consists of superficial violaceous erosions that may be lined by white glassy reticulated papules and plaques, extending into the vaginal vestibule in 70% of cases.<sup>5</sup> A study of 58 women with erosive LP in Norway showed vaginal synechiae in 29 women and total obliteration of the vagina in 9 women.<sup>20</sup> Extensive disease may lead to adhesions and distortion of vulvar architecture, which

may obliterate the vaginal canal, causing difficulty with speculum examination or sexual intercourse.<sup>5</sup> One may also see discharge or contact bleeding on physical examination. If erosive LP is suspected, one should investigate the gingival mucosa for signs of white, lacy reticulations, which may also be seen on buccal mucosa and tongue in classic LP.<sup>17,21</sup> Lichen planopilaris consists of scarring hair loss with perifollicular scale and erythema and may be seen in conjunction with vulvar LP.

## DIAGNOSIS

Vulvar LP has been associated with autoimmune diseases; thus, one might consider checking hemogram, vitamin B<sub>12</sub>, TSH, and blood glucose. There is a general consensus to check viral hepatitis serologies only in cutaneous form of LP.<sup>22</sup> If one suspects fungal or bacterial superinfection, cultures should be taken and appropriate treatment undertaken. LP is most commonly misdiagnosed as LS. However, the vaginal involvement is more typical for LP, contrary to more atrophic, “cigarette paper”-like patches of LS. Other disorders in the differential diagnosis of LP include immunobullous diseases, such as mucous membrane pemphigoid, pemphigus vulgaris, and linear IgA bullous diseases, since they may present with erosions. However, contrary to the immunobullous diseases, the vulvar LP will rarely present with bullae or vesicles.<sup>2</sup> If the patient’s history supports recent exposure to beta-blockers, methyldopa, penicillamine, quinidine, NSAIDs, sulfonyleurea agents, carbamazepine, lithium, allopurinol, and tetracyclines, one might consider lichenoid drug reaction and erythema multiforme in differential diagnosis.<sup>2</sup>

When clinical differential diagnosis is broad and the patient consents to a biopsy, a punch biopsy with direct immunofluorescence is recommended for definitive diagnosis. One should biopsy the border of an eroded area.<sup>5</sup> The typical histology shows irregular epidermal acanthosis, hypergranulosis, some liquefaction degeneration of the basal layer, and a lichenoid infiltrate of lymphocytes. Degenerating keratinocytes, known as colloid bodies, may also be seen near the dermal-epidermal junction.<sup>17</sup> Basal keratinocyte changes in vulvar LP may be mistaken for vulvar intraepithelial neoplasia (VIN), which can lead to a diagnostic pitfall and unnecessary surgery.<sup>1</sup> In erosive disease, the stratum corneum may be lost. In hypertrophic disease, one will see hyperkeratosis along with acanthosis. The DIF will exclude disorders like pemphigus vulgaris (Fig. 61.4).

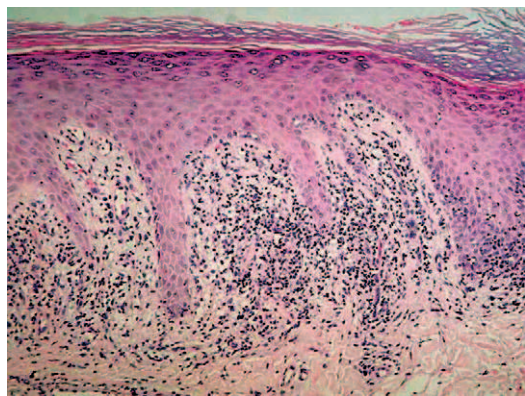
## TREATMENT

Corticosteroid ointments are typically the mainstay of treatment for vulvar LP. Ultra potent steroids like clobetasol propionate 0.05% should be used daily until all active lesions have resolved.<sup>2</sup> Ointments are preferable to creams.<sup>17</sup> A study of 114 women with erosive vulvar LP showed that 71% improved with corticosteroid treatment; some patients also benefited from combined therapy of corticosteroids with antimicrobials or antifungal treatments.<sup>23</sup> When vaginal disease is present, 25 mg hydrocortisone suppositories twice daily may be used



**Fig. 61.3:** Vulvar lichen planus. *Courtesy: Andrew Goldstein, MD.*





**Fig. 61.4:** Histopathology in lichen planus. *Courtesy: Andrew Goldstein, MD.*

to alleviate symptoms.<sup>17</sup> Multiple studies have demonstrated success in treating disease with topical calcineurin inhibitors such as tacrolimus.<sup>13</sup> With more extensive disease, systemic immunomodulators have been attempted in small-case numbers. Prednisone beginning at 40–60 mg daily for 2–4 weeks is a reasonable start point.<sup>13</sup> Other medications which have been used in small studies include hydroxychloroquine, oral retinoids, methotrexate, cyclophosphamide, and mycophenolate mofetil.<sup>13,24</sup> One case report documented improvement of vulvar as well as oral and cutaneous LP with adalimumab within 6 weeks and almost full resolution after week 22.<sup>25</sup> Another report documented a response of extensive erosive oral and genital LP to cyclosporine at 300 mg daily within 6 weeks.<sup>26</sup> Just as with vulvar LS, surgical intervention may have its role when significant architectural distortion has happened.<sup>2,27</sup> Experienced clinicians have had some success in symptom control with lidocaine gel, oral analgesics, and low-dose antidepressant therapy at night time.<sup>16</sup>

## Dermatitis and Lichen Simplex Chronicus

Vulvar dermatitis is a commonly seen pathology, seen in 20–30% of patients in a vulvar clinic.<sup>28</sup> The disorder may be a manifestation of endogenous dermatitis such as atopic dermatitis or seborrheic dermatitis, exogenous dermatitis including allergic contact or irritant contact dermatitis, or the more chronic form known as lichen simplex chronicus (LSC), caused by persistent itching and scratching.<sup>5</sup> Furthermore, anxiety and depression may play a role in worsening the itch-scratch cycle to perpetuate these types of dermatoses.<sup>29,30</sup> LSC may not only be caused by dermatitis, but may also be the result of chronic candidiasis, psoriasis, LS, parasite infection, or neoplasia.<sup>5</sup> In a study of 38 patients with vulvar dermatitis, 97% had underlying atopic dermatitis or seborrheic dermatitis,<sup>28</sup> thus it is believed that an endogenous predisposition occurs in most patients.

### Clinical Presentation

Patients give a history of vulvar pruritus, soreness, and often dyspareunia. Patients with LSC in particular may experience unconscious scratching while sleeping, called the Penelope

phenomenon.<sup>5,29</sup> Given the prevalence of underlying atopy in this group, a clinician should acquire a history of allergies, asthma, or eczema. Thorough questioning may also reveal a history of contact allergies to substances commonly applied to the vulva. It is prudent to ask about possible skin irritation from sweat or urine, particularly in the elderly women. Excess moisture on perineal skin along with urine can significantly increase the pH of the skin, deteriorating the acid mantle which protects from infection and irritation.<sup>31</sup> One should specifically ask about vaginal itching and discharge since trichomoniasis and candidiasis are prevalent disorders that could lead to vulvar symptoms.<sup>32</sup>

The clinical presentation may range from acute bright erythema with crusting and excoriations to more chronic form of LSC, characterized by gray or brown-pink labia majora with cobblestone pattern, loss of hair and lichenification (Fig. 61.5).

LSC may also lead to hypo- or hyper-pigmentation of affected skin.<sup>5</sup> To confirm the suspicion of underlying atopy, one should examine patient's entire body for patches of eczema, Dennie–Morgan folds under the eyelids (usually seen in children in acute/subacute presentation), or hand dermatitis. In patients with seborrheic dermatitis, there may be orange-pink patches and thin plaques with fine scale on the mons pubis, labia majora, and the intertriginous area.<sup>31</sup> In addition, there may be greasy yellow scales along the nasolabial folds and within the eyebrows.

### DIAGNOSIS

Usually the physical examination along with the history will lead to a diagnosis of vulvar dermatitis or more specifically to an appropriate subtype of dermatitis, such as atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis, or LSC. The differential diagnosis may include psoriasis and extramammary Paget disease, but both will have more well-demarcated plaques



**Fig. 61.5:** Lichen simplex chronicus. *Courtesy: Andrew Goldstein, MD.*



and can be ruled out by skin biopsy. One should take a fungal and/or bacterial culture of the region if infection is suspected, as candida and group B streptococcus are not unusual. Scraping for scabies may be helpful.<sup>30,33</sup> Early LS may also present similar to vulvar dermatitis; however, the clinical presentation will evolve and exhibit the characteristic appearance of the disease.

A laboratory workup is usually only performed if other diagnoses are suspected, although one study showed that 20% of patients with vulvar dermatitis had a low serum ferritin, and their symptoms improved with iron supplementation. Thus, checking a serum ferritin may be prudent if history of vegetarianism, blood donation, or previous anemia is given.<sup>28</sup>

If a contact allergen is suggested by the history, patch testing may be performed. Relevant contact allergies were found in 26% of patients with vulvar dermatitis and included fragrances to toiletries, formaldehyde and its releasing preservatives, and Kathon CG, a preservative.<sup>28</sup> Another prospective study of 43 patients with vulvar pruritus revealed 44% prevalence of relevant contact allergies, with the most common allergen being Vagisil (benzocaine, resorcinol, methyl hydroxybenzoate, or sodium sulfite anhydrous).<sup>34</sup> Though contact dermatitis is often suggested by history and physical examination, a biopsy will show spongiosis, acanthosis, parakeratosis, and a dermal inflammatory infiltrate, and in a more chronic condition, one may see hyperkeratosis and hypergranulosis.<sup>35</sup>

## TREATMENT

As with dermatitis seen in other areas of the body, treatment is geared at reducing irritants, reducing inflammation, and improving the skin barrier. If a contact allergen or irritating product is found to be the culprit, the patient must stop the use of that agent. Fragrances should be eliminated from products used to clean or wipe the vulva. If the irritant is urine or sweat, absorbing powders, zinc oxide cream, or absorbing diaper products may reduce exposure. Discontinuing use of tight slacks and undergarments may reduce sweating as well.<sup>35</sup> To reduce inflammation, topical corticosteroids and topical calcineurin-inhibitors (tacrolimus, pimecrolimus) may be used.<sup>5</sup> Open label studies with pimecrolimus have shown efficacy in treating LSC, without the risk of skin thinning as with corticosteroids.<sup>13</sup> In addition, scratching—one of the biggest inducers of inflammation—may be reduced with patient education and palliative measures such as lidocaine gel, sitz baths, and ice pack.<sup>5,35</sup> To improve the skin barrier, emollients such as petrolatum or vegetable oil should be used liberally; this may be particularly important in the post-menopausal and elderly women with significantly increased transepidermal water loss.<sup>36</sup> In addition, some gynecologists prescribe topical estrogen preparations for vulvo-vaginal use in the perimenopausal women, potentially increasing the possibility of endometrial hyperplasia.<sup>36</sup>

To improve the overall discomfort of the patient, antihistamines such as hydroxyzine or diphenhydramine may be used at bedtime.<sup>37</sup> Patients might also benefit from tricyclic antidepressants such as amitriptyline 25 mg at bedtime.<sup>5</sup>

## Psoriasis

Psoriasis is a chronic inflammatory skin disease rarely limited only to the genitals; however, the genital disease is often the most recalcitrant to treatment and can have significant physical and psychological impact on the patient. Often the practitioner must specifically ask the patient with psoriasis about lesions on the genitals or that information will not be volunteered. This may be particularly true in the pediatric population, which may present with vulvar psoriasis more often than adults.<sup>38</sup>

## CLINICAL PRESENTATION

The clinician may suspect vulvar psoriasis if the patient has a personal or family history of psoriasis or has a positive review of systems for joint stiffness or pain.<sup>39</sup> Yet, a diagnosis of vulvar psoriasis will most often be made through physical examination. On the mons pubis and the labia majora, one will usually see smooth well-demarcated or sometimes beefy red scaly plaques. However, there is an absence of typical silvery, micaceous scale seen on the trunk or extremities since the vulva is better hydrated than other sites of the body.<sup>31</sup> Only the hair-bearing genital skin is affected by psoriasis, which excludes the labia minora and other mucosal structures. The erythematous plaques may extend toward the perianal and intergluteal cleft region (Fig. 61.6).

One may see other signs of psoriasis on full skin examination, including well-demarcated plaques on the scalp, elbows, knees, or trunk. If the patient has inverse/flexural psoriasis only, the disease may be limited to the genital areas, umbilicus, and axillae.

## DIAGNOSIS

A diagnosis of vulvar psoriasis may be obvious in the case of a patient with a history of psoriasis; however, one may also need to rely on the lesion morphology. If seborrheic dermatitis and psoriasis are seen together in the same patient, one may use the term “sebopsoriasis.” If the lesions are confluent and affect the groin area as well as the labia majora, one might consider tinea cruris, especially if there is festooning border, pustules, or worsening of lesions with use of topical steroids. A potassium



**Fig. 61.6:** Vulvar psoriasis. *Courtesy: Jennifer Powers, MD.*

hydroxide examination of the scraping of the scale should establish the diagnosis.

## TREATMENT

First-line treatment is generally a moderate potency topical corticosteroid, pulsed daily for use when needed and stopped when disease is controlled. However, since corticosteroids may thin the already delicate skin of the groin, topical calcineurin-inhibitors may also be the first-line treatment. Tacrolimus ointment 0.1% has been shown to reduce erythema, desquamation, and infiltration of flexural psoriasis including genital disease.<sup>40</sup> One should treat fungal or candidal superinfection if suspected. Though vulvar psoriasis is typically viewed as a non-scarring process, there have been a few cases described in which biopsy-proven vulvar psoriasis led to scarring of the labia minora as well as sealing of the clitoral hood.<sup>41</sup> This may underscore the importance of treatment, for the disease both in the present and the future.

## Immunobullous Diseases

Acquired autoimmune blistering diseases were associated with tremendous mortality until the development of oral corticosteroids in the 1950s. These disorders, including pemphigus vulgaris (PV), bullous pemphigoid (BP), mucous membrane pemphigoid (MMP), and chronic bullous disease of childhood (CBDC), can affect the female genitalia, though they do not usually affect the vulva exclusively. BP is the most common of these disorders.<sup>31</sup> PV is more commonly seen in people of Ashkenazi Jewish descent with a yearly incidence of 0.1–3.2 cases per 100,000 people.<sup>42</sup> With the exception of CBDC, which is often seen in children, the other disorders affect primarily older adults, particularly the elderly. These disorders share a common pathophysiology in which antibodies bind to building blocks of the epidermis or basement membrane, leading to immune dysfunction and subsequent blister formation. The targets of Immunoglobulin G (IgG) in PV, BP, and MMP are desmoglein 3, BPAG1/2, and BPAG2, respectively.

## CLINICAL PRESENTATION

Patients with immunobullous diseases in their early stages may not present with frank blisters but may have plaques or itching. If the disease is fully developed, then one should note blister locations and whether the bullae are tense or flaccid. If the bullae have been traumatized or are healing, the clinical examination may be positive only for erosions, often crusted. All mucosal sites including eye, mouth, genitals, and anus should be examined for blisters, erosions, and other lesions. If patients have lesions in the mouth, there may be significant decrease in oral intake of foods or liquids. Nikolsky sign, in which upper layers of the skin move laterally with slight pressure, or the Asboe-Hansen sign, in which pressure on an intact bulla moves fluid under nearby and seemingly uninvolved skin, may be seen in these disorders. The diagnosis will be based on a full history and total body-skin examination.

PV will present with flaccid bullae on the skin and oral mucosa, the latter of which is usually the first site of involvement, particularly on the buccal and palatine mucosa.<sup>31</sup> Because these flaccid bullae easily give way to denuded erosions, these patients often complain of significant pain at the site of disease activity. The erosions may be of varying sizes with irregular borders. Vulvar mucosa is infrequently involved, because the antigen desmoglein 3 is found in higher concentration in other sites including the mouth rather than the genital area.<sup>31</sup> In a retrospective review of cases of female genital PV, 38% of patients had vaginal involvement, particularly in the distal one-third of the vagina. If such disease is suspected, one should perform a pelvic examination to determine the extent of involvement.<sup>42</sup>

BP begins with itching and urticarial plaque formation on the trunk, extremities, and flexural sites many months before any blistering begins.<sup>31</sup> When bullae appear, they are tense with erythematous borders and often symmetrical with higher propensity for flexural surfaces. If lesions appear on the vulva, they may become eroded due to frictional forces. Long-standing lesions may be hemorrhagic. In children, lesions may be localized to the vulva.<sup>43</sup> BP may also be associated with an underlying malignancy, so a good review of systems should be taken to evaluate a need for further work up.

MMP, also known as cicatricial pemphigoid is almost always associated with ocular and oral involvement, often presenting with erosive desquamative gingivitis. With early disease, the conjunctivae may be injected, causing pain or a foreign-body sensation; with later disease, scarring of the palpebral conjunctivae to the bulbar conjunctivae may lead to symblepharon formation. The upper aerodigestive tract may also be involved, and skin may be characterized by erythematous plaques or erosions. In MMP with vulvar involvement, patients complain of pain, itching, and dysuria. They may also complain of vision loss, conjunctival injection, and oral discomfort.<sup>31</sup> On physical examination, the labia minora, vaginal vestibule, and introitus may be afflicted with bullae and/or erosions, which may cause architectural distortion with permanent disfigurement.<sup>31</sup> The vulva may appear eroded or with labial fusion in more chronic cases, not unlike erosive LP (Fig. 61.7).

CBDC presents as tense bullae generalized over the body and perioral areas but often also affecting the vulva. The bullae may resemble a “string of pearls” and are marked by an annular, polycyclic appearance and often appear in the flexural areas.

## DIAGNOSIS

One must rule out infectious causes of vesicles and bullae such as HSV infections, particularly when the lesions are limited to the genitals. With vesicular fluid, one may take a viral culture, perform direct fluorescence antibody testing for herpes simplex virus (HSV) 1 and 2, or perform PCR testing for HSV 1 and 2. Lesions of herpes zoster can also occur on the vulva. Bacterial and/or fungal swabs may also be needed to rule out secondary infection as eroded surfaces may easily become colonized with



**Fig. 61.7:** Cicatricial pemphigoid. Courtesy: Andrew Goldstein, MD.

*Staphylococcus aureus*, streptococcus, and candida. If the history is suggestive of unprotected sexual contact or HIV infection, one may also consider Epstein–Barr virus, cytomegalovirus, or syphilis. If erosions, rather than frank vesicles or bullae, are present, then one must also entertain other diagnoses including erosive LP, LS, squamous cell carcinoma, epidermolysis bullosa acquisita, Behcet disease, extramammary Paget disease, or fixed-drug eruption. If bullae and vesicles have been present since childhood, then one might consider inherited forms of bullous disease such as epidermolysis bullosa and Hailey–Hailey disease.

One should perform two skin biopsies—one for H&E staining and one for DIF, the former taken from the lesional skin and the latter taken from peri-lesional skin. On the H&E slide, PV will be characterized by acantholysis above the basal layer of the epidermis along with intraepidermal bullae and may exhibit tombstone phenomenon. DIF will show a “chicken-wire” pattern of fluorescence, highlighting the intraepidermal space surrounding each keratinocyte. BP will be characterized on H&E by a subepidermal bulla filled with eosinophils and neutrophils. DIF will show fine, linear, continuous IgG fluorescence along the basement membrane zone. If salt-split skin is performed, the immune staining will be seen in the roof. MMP will also show subepidermal blister formation on H&E as well as fibrosis in the dermis in older lesions. DIF will show fine linear IgG and/or C3 along the basement membrane zone, and salt-split skin will demonstrate positive staining in the roof. CBDC will be marked by subepidermal vesicles with infiltration of neutrophils. DIF will show linear immunoglobulin A (IgA) deposits along the basement membrane zone, which typically distinguishes the disorder from dermatitis herpetiformis containing IgA in a granular pattern in the dermal papillary tips.

## TREATMENT

The treatment approach for immunobullous diseases is similar but depends significantly on the disease severity. The clinician

should aim to control blistering and discomfort while minimizing side effects from immunosuppression. If disease is limited, then moderate doses of daily prednisone in conjunction with topical clobetasol ointment 0.05% may be adequate. For standard disease, 1.0 mg/kg/day of prednisone can be started. A less traditional approach with fewer side effects may combine oral prednisone with oral nicotinamide and minocycline or doxycycline at 100 mg twice daily. Such antibiotics are often successfully employed in CBDC and BP in which oral steroids are often avoided. When disease activity is moderate to severe, then systemic immunosuppressants such as cyclosporine, mycophenolate mofetil, azathioprine, dapsone, and methotrexate are prescribed. For vulvar lesions in particular, local treatment with corticosteroids either topically or intralesionally (kenalog 15 mg/mL) may be effective.<sup>42</sup> Any concomitant infections should also be treated with appropriate antimicrobials.

## Epidermolysis Bullosa Acquisita

Epidermolysis bullosa acquisita (EBA) is an uncommon chronic severe immunobullous disease, which has been rarely described on the vulva. The clinical and the histological picture, including those of immunofluorescence, are similar to those of BP.<sup>44</sup>

It is caused by IgG autoantibodies directed against the noncollagenous amino-terminal (NC-1) domain of collagen VII, a major component of anchoring fibrils located in the lamina densa and sublamina densa region. Small group of patients demonstrate antibodies to the collagen domain or have IgA antibodies.<sup>45</sup>

## CLINICAL FEATURES

It is characterized by tense, subepidermal vesicles and bullae that heal with scarring and milia. Lesions may appear on any mucocutaneous surface and generally are distributed in anatomic areas subjected to repetitive minor trauma, such as the extensors of upper extremities. Clinical features of EBA are similar to those of BP, however the antibody binds to the floor of the blister, the dermal component.<sup>45,46</sup>

EBA can occur at any age, but it more frequently affects elderly patients. Childhood cases have been reported in the literature. In 1997, Park et al.<sup>44</sup> reported a case of a 6-year-old girl with EBA, who had lesions in the genital area.

## DIAGNOSIS

### Histopathology

Light microscopic examination of the tissue stained with hematoxylin and eosin reveals subepidermal bulla. The degree of associated inflammation on histology correlates closely with the clinical appearance of the lesion selected for biopsy. Classic EBA usually presents with a non- or pauci-inflammatory subepidermal blister, whereas the inflammatory form of EBA is associated with a neutrophil-rich infiltrate with variable



numbers of eosinophils.<sup>45</sup> Because histological findings of EBA are nonspecific, immunofluorescence and other testing modalities are required for definitive diagnosis.

### Immunofluorescence

DIF studies of perilesional skin demonstrate IgG, and to a lesser extent C3, deposits distributed in a thick continuous and linear pattern along the epidermal basement membrane zone. Less commonly linear deposits of IgA or IgM are found.

Indirect immunofluorescence (IIF) is approximately positive in about half of the affected patients. IIF reveals the presence of circulating IgG autoantibodies in the patient's serum that target type VII collagen of the basement membrane. IIF on salt-split normal human skin illustrates the binding of the circulating antibodies to the dermal side (lower part) of the artificial blister. IIF on salt-split skin helps differentiates EBA from BP, in BP IgG autoantibodies from the serum bind to the epidermal roof (upper part) of the bulla.<sup>45,46</sup>

### Differential Diagnosis

EBA must be differentiated from other diseases associated with subepidermal blisters like BP, MMP, porphyria cutanea tarda, bullous form of lupus erythematosus and dominantly inherited epidermolysis bullosa dystrophica.

### Management

The prognosis of EBA is very variable, but rarely life-threatening. The treatment of this chronic blistering dermatosis is challenging because of the rarity of the condition combined with the absence of published randomized, controlled therapeutic trials.

Options of treatment include systemic corticosteroids, other immunosuppressive agents, such as azathioprine, methotrexate, and cyclophosphamide. Because of its relatively benign side effects, colchicine has been used successfully in some patients. Dapsone, mycophenolate mofetil, rituximab, intravenous immunoglobulin, or cyclosporine have also been reported to have some benefit. Extracorporeal photochemotherapy may be helpful in EBA patients unresponsive to conventional therapy.<sup>45,46</sup>

### Hidradenitis Suppurativa “Acne Inversa”

Hidradenitis suppurativa (HS) is a chronic condition characterized by recurrent boils, sinus tracts formation and subsequently leading to scarring. HS occurs in the apocrine-bearing skin, such as the axillae, buttocks, groins, mammary and inframammary regions. In the female genital region it often affects the labia majora and natal cleft. It occurs in obese individuals, although this is not always the case. There may be a family history of this condition.<sup>47</sup>

HS was felt to be due to apocrine gland activity, but now it is recognized to be essentially follicular, we now know that occlusion of the follicular infundibula followed by rupture of the follicle is the inciting event.

In some patients, HS makes up one part of follicular occlusion syndrome when it is associated with acne conglobata, dissecting cellulitis, and pilonidal sinus.<sup>47</sup>

Some authors recommend abandoning the use of the name hidradenitis suppurativa and replace it with “acne inversa.” The term acne inversa links the pathogenesis to acne and reflects the fact that it is an expression of follicular occlusion in localizations inverse to acne vulgaris.<sup>48</sup>

### Epidemiology

HS starts around puberty and coincides with the post-pubertal increase in androgen levels. Average patient age is 23 years. Children are not affected unless they have precocious puberty. Women are affected three times as often as men.<sup>47</sup>

### Clinical Features

HS is characterized by the presence of painful subcutaneous nodules; with time these nodules may rupture resulting in deep dermal abscesses. After rupture, the lesions often extrude a purulent, foul smelling discharge. As the disease process continues, fibrosis, dermal contractures, and induration of the skin occur. The presence of double comedones is typical of the disease.<sup>47–49</sup>

### Histology

Follicular occlusion is prominent with keratin plugs, with dilatation of the follicular infundibulum. There is superficial and deep dermal perivascular infiltrate of neutrophils, lymphocytes, histiocytes, and plasma cells. Rupture of follicles results in perifollicular abscess, granulation tissue, and foreign-body giant cell reaction. Secondary involvement of apocrine glands occurs with dilatation of the glands and infiltrate of neutrophils in the walls and within the lumen.<sup>47,50</sup>

### Differential Diagnosis

In the early stages, a simple folliculitis may be suspected, but this usually has central pointing or ulceration and usually does not form sinus tracts. Other conditions with similar features include dermoid cyst, cutaneous blastomycosis, furuncles and lymphadenopathy.

In the chronic indurated lesions, often with sinus formation, Crohn disease should be considered. The two diseases may coexist. Other conditions, including granuloma inguinale (donovanosis), mycetoma, lymphogranuloma venereum, nocardial infection, noduloulcerative syphilis, and tuberculosis may resemble HS.<sup>47</sup>

### Management

Diabetes mellitus should be excluded. Medical treatment includes weight reduction if the patient is overweight. Intralesional injection of steroids may be helpful in early inflammatory lesions. Topical antibiotics, like clindamycin have proven beneficial in some patients.<sup>47,49</sup>

Systemic antibiotics, either alone or in combination are used. Recently, a combination of clindamycin and rifampicin has been suggested. Oral retinoids may have a role to play in the management of this disease. Systemic corticosteroids often lead to dramatic improvement. Dapsone was shown to be effective in some patients. Immunosuppressive drugs, like cyclosporine could be beneficial. The TNF-alpha inhibitors infliximab and etanercept have also produced favorable outcomes in HS.<sup>47,49</sup>

The best results seem to occur when the involved areas are surgically excised and closed primarily or grafted. The earlier in the course of the disease excision is performed the better. However, recurrence of the disease may be problematic. CO2 laser has been used successfully in HS, as well as Botulinum toxin A injection.<sup>47,49</sup>

## COMPLICATIONS

Observation and follow-up is necessary as a small number of these patients progress to develop malignancy, squamous cell carcinoma within the non-healing sinus tracts.<sup>51-53</sup>

The excessive scarring and fibrosis produced by HS lesions can lead to contractures and limitations in limb mobility, especially in the axilla.<sup>47,49</sup> In addition, inflammation and scarring in the genital region may predispose to anal, urethral, and rectal strictures. Urethral fistulas and vulvar lymphedema have also been reported in patients with HS.

## Crohn's Disease

Vulvar Crohn disease (CD) can present as an extension of gastrointestinal (internal) disease or metastatic CD (MCD). The condition has been reported in patients as young as 8 years old to 64 years old.<sup>54</sup> Nearly two-thirds of patients are premenopausal women.

## PRESENTATION

The presentation of vulvar CD is usually varied and difficult to diagnose, especially in cases of metastatic spread rather than direct or contiguous spread such as from fistula formation. In a recent review, metastatic spread was found to be by far the most common presentation, in 91% of cases (50 patients out of 55), while contiguous spread occurred in only 9% of the cases (5 patients).<sup>55</sup>

The length or specific "type" of previously active CD was not identified to predispose patients to CD of the vulva. Interestingly, 25% of patients with vulvar CD did not have any previous intestinal symptoms and had not been diagnosed with CD at the time of their vulvar symptoms.<sup>55</sup>

Involvement of the vulva can be the first and/or the only manifestation of disease.

Furthermore, vulvar CD can appear many years after a subtotal colectomy in patients with evidence of no other CD<sup>56</sup> or can persist despite excision of the intestinal disease or quiescent gastrointestinal disease.<sup>57</sup>

## SIGNS AND SYMPTOMS

There is no consistent correlation between the appearance of cutaneous lesions and intestinal disease activity.

CD of the vulva typically manifests with swelling, pruritus, erythema, and as a progressive and painful ulceration of the labia. These can often evolve into condyloma-like lesions and/or skin tags. Patients can also present a wide range of symptoms such as vaginal discharge, painful ulcerations, or a vulvar mass (Table 61.2).<sup>55</sup> Physical examination usually reveals an indurated area, localized or generalized edema of the labia, and ulcers that often extend into the groin. These signs and symptoms are also common to many other gynecological conditions making the clinical suspicion of vulvar CD very difficult. This results in delayed definitive diagnosis.<sup>58</sup>

## DIAGNOSIS

When these clinical features are identified, it is important to exclude other granulomatous diseases such as sarcoidosis, tuberculosis, lymphogranuloma venereum, pyogenic infections, HS, intertrigo, and syphilitic lesions. A biopsy of the lesion shows the typical non-caseating granulomas.

## DIFFERENTIAL DIAGNOSIS

The absence of comedones and bridging scars differentiates CD from HS. There may be no clinical evidence of bowel disease, but the edema and multiplicity of physical signs is often very suggestive of CD.

## TREATMENT

The natural course of vulvar CD is unpredictable. Some lesions may resolve spontaneously. The treatment relies mainly on medical therapy.

Systemic antibiotics such as ciprofloxacin and metronidazole may be helpful in managing the acute-on-chronic episodes in this nasty disease. The most successful treatment was achieved by metronidazole alone or in conjunction with oral or topical steroids with a success rate of 87.5%.<sup>55</sup> Systemic, intralesional, and topical corticosteroids,

**Table 61.2:** Signs and Symptoms at Presentation of 55 Cases with Vulvar Crohn Disease

Symptom	Total no. of patients (percentage)
Swelling	34 (61.8)
Ulcers	22 (40.7)
Pain	11 (20.3)
Pruritus	7 (12.9)
Erythema	8 (14.5)
Abscess	2 (3.7)
Discharge	3 (5.5)
Mass	2 (3.7)

Adapted from Andreani et al.<sup>55</sup>

5-aminosalicylic acid, and sulfasalazine are also among the medical therapies purported to be of benefit for MCD.<sup>59</sup>

Immunomodulating therapies, including the use of mercaptopurine, azathioprine, and anti-tumor necrosis factor, are being used in the medical management of CD.<sup>60</sup>

Surgical therapies for MCD have been tried for resistant cases. However, correlation between the appearance of cutaneous lesions and intestinal disease activity is quite variable<sup>61</sup>; thus, it is not surprising that surgical removal of diseased bowel does not always result in the improvement of MCD.

Surgical debridement of perianal CD was shown to be beneficial in those patients with co-existing abscess of the vulva.<sup>55</sup> Bowel surgery may be helpful, and in most unpleasant cases, vulvectomy may have to be resorted to,<sup>62</sup> although the cutaneous disease does tend to recur. The disease should be closely monitored, as cancers have been described.<sup>63</sup>

### Zoon Vulvitis (Vulvitis Circumscripta Plasma Cellularis or Plasma Cell Vulvitis)

This rare, chronic, benign inflammatory condition is much less common in women than its counterpart in men, Zoon balanitis. It was described both by Zoon in 1954 and Garnier in 1955.<sup>64,65</sup> Since that time, 34 cases of Zoon vulvitis have been reported in the literature in women ranging in age from 8 to 79 years. Its precise incidence is unknown.<sup>66</sup>

#### CLINICAL FEATURES

The condition may initially be asymptomatic. Symptoms include pruritus, dyspareunia, and dysuria. Clinically, these lesions are circumscribed, glistening, erythematous macules with a yellow or orange hue, occasionally with purpuric spots described as “cayenne pepper”<sup>66,67</sup> (Fig. 61.8). The lesions can be found on the labia minora and majora, clitoris, posterior fourchette, and urethral meatus.

#### ETIOLOGY

The exact etiology is unclear, but suggested predisposing factors include warmth, friction, poor hygiene, and herpes simplex and other chronic infections.<sup>65,66</sup>

#### HISTOLOGY

Zoon vulvitis is characterized by the dense subepithelial band-like (lichenoid) infiltrate with plasma cell predominance as the main histological feature. Epidermal thinning with small horizontally disposed lozenge-shaped keratinocytes, mild spongiosis, vascular dilatation, and red cell extravasation with hemosiderin deposition are considered further distinctive criteria. While reactive epithelial changes may be present, true dysplasia is absent.<sup>67</sup>

#### DIFFERENTIAL DIAGNOSIS

The differential diagnosis should include Paget disease, pemphigus vulgaris, LP, fixed drug eruption, squamous carcinoma, and herpes



**Fig. 61.8:** Plasma cell vulvitis, with beefy erythematous plaques. *Courtesy: Andrew Goldstein, MD.*

simplex infection. The diagnosis should be considered in any patient with an erythematous lesion and intractable vulvar pruritis.<sup>65,66</sup>

#### MANAGEMENT

Response to therapy is inconsistent. Reported treatments include topical,<sup>67</sup> intralesional and systemic corticosteroids, antifungal agents, antibiotics, etretinate, interferon, vaginal estrogen, topical calcineurin inhibitors (Tacrolimus),<sup>68</sup> and immunosuppressive agents. Destructive modalities like fulguration, laser ablation, cryotherapy and surgical resection have been suggested. To date there are two cases that cleared completely after using high potency topical steroids.<sup>69</sup>

### Behçet Disease (BD)

This disease was named in 1937 after the Turkish dermatologist Hulusi Behçet, who first described the triple-symptom complex of recurrent oral aphthous ulcers, genital ulcers, and uveitis.<sup>70</sup> Later, it was recognized as a multisystem disease. The diagnosis is made on the basis of criteria proposed by the International Study Group for Behçet syndrome in 1990.<sup>71</sup> In order that a diagnosis of Behçet syndrome might be made, oral ulceration will exist in association with two of the following: recurrent genital ulceration, cutaneous lesions and eye lesions, and a positive pathergy test.

Table 61.3 describes the criteria required for the diagnosis of Behçet syndrome.

Bipolar aphthosis of Neumann is considered as a *forme fruste* of BD. It is characterized by oral and genital ulcers without any other manifestations. BD is most prevalent (and more virulent) in the Mediterranean region, Middle East, and Far East.<sup>72</sup>



**Table 61.3:** International Study Group Criteria for Behçet Disease

Finding	Definition
Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulcers observed by the physician or patient, which have recurred at least three times over a 12-month period
Recurrent genital ulceration	Aphthous ulceration or scarring observed by the physician or patient
Eye lesions	Anterior uveitis, posterior uveitis, or cells in the vitreous on slit-lamp examination; or retinal vasculitis detected by an ophthalmologist
Skin lesions	Erythema nodosum observed by the physician or patient, pseudofolliculitis, or papulopustular lesions; or acneiform nodules observed by the physician in a post-adolescent patient who is not receiving corticosteroids
Positive pathergy test	Test interpreted as positive by the physician at 24 to 48 hr

### ETIOLOGY

Susceptibility to BD is strongly associated with the presence of the human leukocyte antigen (HLA)-B51 allele and its presence is also strongly associated with a more aggressive course. The cause of BD is however still unknown. Infections, both viral and bacterial, may play a role.<sup>72</sup>

### CLINICAL PRESENTATION

The genital ulcers are seen in about 60–90% of patients with Behçet syndrome and morphologically resemble oral aphthae. The ulcers are painful and heal with scarring.<sup>72</sup>



**Fig. 61.9:** Vulvar ulceration in patient with Behçet disease. Courtesy: Andrew Goldstein, MD.

These ulcers can be located on the vulva, vagina, cervix, or groins, but the most common location is on the vulva (Fig. 61.9). Ulcers on the female patient tend to be larger and deeper than in the males with genital lesions, sometimes even leading to perforations. When located in vagina, they may lead to urinary/fecal fistulae formation. The size of these ulcers is usually 1–2 cm.<sup>72,73</sup>

Superadded sexually transmitted infection may be a concern as the epithelial barrier is lost in recurrent genital ulcers due to BD.<sup>74</sup> Intractable postcoital bleeding due to Behçet vaginal ulcer requiring surgical intervention has been reported in a woman.<sup>75</sup>

### MANAGEMENT

Usually the ulcerations heal spontaneously. With regard to treating the symptoms and healing of genital aphthae, local treatments as described for aphthae may be used. Topical steroids are usually effective for mucocutaneous involvement. Some patients respond insufficiently and additional treatment may be necessary in these cases.<sup>76</sup>

Colchicine is known to be beneficial in mucocutaneous disease,<sup>77</sup> in a double-blind trial with 116 patients in 2001,<sup>78</sup> Yurdakul and colleagues found that colchicine reduced the occurrence of genital ulcers, erythema nodosum, and arthritis in both men and women. Other available alternatives like aspirin, dapsone, levamisole, thalidomide, cyclosporine, interferon-alpha (IFN-alpha) and TNF blockers have all been reported to be helpful.<sup>72,76</sup>

### Aphthous Ulcers

Aphthous ulcers can present as minor and major type. The latter is associated with more severe pain and scarring. The etiology is unclear. Some believe that these ulcers are a result of a dysfunction of the immune system, resulting in immunologically mediated damage to epithelial cells. This reaction may be triggered by trauma, hematinic (e.g., iron, folate, or vitamin B<sub>12</sub>) deficiencies, hormonal fluctuations, psychological stress, infectious agents, food hypersensitivities, genetic factors, and HIV infection. The lesions are recurrent and they may correlate with the menstrual cycle.<sup>79</sup>

### CLINICAL FEATURES

As a rule, aphthous ulcers are painful, they are mostly 5 mm in diameter but may vary in size from 3 to 10 mm (larger ulcers are termed major aphthae). The ulcers are round, shallow, and sharply defined with a yellow base and a red halo. Usually one to five lesions occurs per attack; however, they may occur in any number. The lesions tend to involute in 1–2 weeks, but recurrences are common<sup>79</sup> (Figs. 61.10a and 61.10b).

### HISTOPATHOLOGY

Histopathological examination of the biopsy specimen does not reveal unique findings and is rarely indicated, except to exclude other diagnoses, such as pemphigus, cicatricial pemphigoid,



\*c+



\*d+

**Figs. 61.10(a) and (b):** Vulvar aphthous ulcers. *Courtesy: Andrew Goldstein, MD.*

carcinoma, and BD. Histologically, the lesions consist of dense perivascular and interstitial lymphocytic inflammatory infiltration in the sub mucosa with occasional plasma cells.<sup>79,80</sup>

### DIFFERENTIAL DIAGNOSIS

Includes common viral infections (e.g., HSV), physical trauma, autoimmune blistering disorders (e.g., pemphigus vulgaris, cicatricial pemphigoid), LP, and erythema multiforme. In the case of multiple major mucosal aphthous ulcers (oral and genital), it might be difficult to distinguish this condition from BD. Extensive and painful aphthosis may occur in patients with HIV.<sup>80</sup>

### MANAGEMENT

No cure is available. Several topical agents will lessen the pain. Locally applied corticosteroids usually improve the patient's

symptoms. Application of topical anesthetics, like 5% lidocaine ointment, are useful. In severe cases, systemic therapy with dapsons, colchicine and thalidomide have been used.<sup>80</sup>

## Pyoderma Gangrenosum

Pyoderma gangrenosum (PG) is a rare cause of vulvar ulceration. There are few cases of vulvar involvement described in the literature.<sup>81–83</sup> It is important to differentiate this from an infective lesion as the treatment of PG is with systemic corticosteroids and immunosuppressive agents.

### CLINICAL FEATURES

PG manifests as painful cutaneous ulceration with undermined edges, irregular margins, ragged purple overhanging edge and necrotic tissue at the base. Lesions can present as single or multiple small ulcers.

Classic PG begins as an inflammatory pustule with a surrounding halo that enlarges and begins to ulcerate. A primary lesion may not always be seen, and a substantial proportion of lesions appear at the sites of trauma (pathergy).<sup>81–83</sup>

### ETIOLOGY

The pathophysiology of PG is unknown, but altered immune system is believed to be involved. Most common is an association with systemic diseases, especially arthritides (seronegative and seropositive), inflammatory bowel disease and hematological disorders (leukemia and monoclonal gammopathies). Less commonly associated diseases include hepatic diseases, myelomas, immunological diseases, and HIV infection. Screening tests for underlying diseases should be performed.

### HISTOLOGY

There may be signs of vasculitis, but most commonly only chronic inflammation is seen.

Early histopathological feature is dermal neutrophilic abscess; later biopsies demonstrate epidermal necrosis and ulceration, superficial dermal edema, and a dense, mixed dermal infiltrate. Histopathological findings are not specific but crucial to rule out other causes of skin ulcers.<sup>84</sup>

### DIFFERENTIAL DIAGNOSIS

The clinical picture of PG, in the classic ulcerative form, is characteristic. As there are no diagnostic serological or histological features, PG mostly remains a diagnosis of exclusion.

Multiple infections (e.g., viral: herpes, bacterial: cellulitis), syphilis must be excluded. Various forms of cutaneous vasculitis, vulvar ulcerations in patients with BD and other types of neutrophilic dermatoses like Sweet syndrome may produce similar clinical picture.<sup>85</sup>

## TREATMENT

Associated underlying conditions should be sought, even if no symptoms are found. The nature and intensity of the therapeutic approach depend on the number, size and depth of the lesions, the rate of expansion and appearance of new lesions, the associated disorder, the medical status of the patient, and the risk and patient's tolerance of prolonged therapy.

The standard treatment of PG is local or combined local and systemic corticosteroid therapy with or without adjunctive systemic immunosuppressive therapy.

In mild cases, application of topical corticosteroid, intralesional steroid injections, or topical tacrolimus may be beneficial. Systemic high dose corticosteroids can be very effective. A dramatic improvement with corticosteroid treatment supports the diagnosis of PG.

Other alternative systemic treatments, used in cases resistant to corticosteroids or in cases with severe corticosteroid side effects, are cyclosporine A, azathioprine, cyclophosphamide, and chlorambucil, which have been reported to be effective. Cyclosporine and infliximab result in faster healing and are considered the immunosuppressives of choice for managing severe or refractory PG.<sup>81–84</sup>

## Lupus Erythematosus

The prevalence of vulvar involvement in patients affected with systemic lupus erythematosus (LE) is unknown, and there are a limited number of cases in the literature on genital lupus.

In 1989, Burge et al.<sup>86</sup> published a series of reports on 121 patients affected with lupus (both males and females), the group found that 21% of patient with systemic lupus and 24% of those with chronic cutaneous LE (CCLE) had mucosal involvement. There were no specific genital lesions found in 48 females with systemic LE, although one patient had vaginal lesions possibly secondary to Sjogren syndrome. However, vulvar lesions were identified in 2 of 42 patients with CCLE. One patient had erythema and painful ulceration near the vaginal introitus, while the other had lacy LP-like plaques on the vulval mucous membranes.

Discoid lupus lesions have been reported on the female genitalia. Bilenchi in 2004<sup>87</sup> reported a case of a patient with history of discoid LE, who developed discoid lesions on the labia majora. Jolly and Patel in 2006<sup>88</sup> reported a single case of a patient with systemic LE who developed discoid LE lesions on the left labium majus (Fig. 61.11).

## Dermatomyositis

In 1985, Lavery et al.<sup>89</sup> reported the only case in the literature of dermatomyositis involving the vulva. Dermatomyositis may be associated with an underlying malignancy, and Celebi et al. in 2001<sup>90</sup> reported a case of its occurrence in a patient with cervical carcinoma. Wishart in 1973<sup>91</sup> reported a case of a 42-year-old female with dermatomyositis who developed reticular cell sarcoma (reticulosarcoma) of the vulva after five months of azathioprine therapy.



**Fig. 61.11:** Clinical appearance of discoid genital plaque in a patient with systemic lupus erythematosus. With permission from Jolly M and Patel P.<sup>88</sup>

## Estrogen-Mediated Cyclical Vulvitis

Fischer et al. in 2000<sup>92</sup> has described a group of women who had either treatment resistant cyclical vulvitis or a vulvitis provoked by hormone replacement therapy (HRT). Intradermal testing with endogenous estrogens demonstrated delayed type hypersensitivity responses. Two of the patients reacted to intradermal testing with progesterone.

## DIFFERENTIAL DIAGNOSIS

Candidal vulvitis and Zoon vulvitis should be differentiated with appropriate swabs and biopsies.

## MANAGEMENT

In this small group described above, one improved at menopause. Those with HRT provoked disease resolved on cessation of HRT. Three responded to lowering their endogenous estrogen levels, and one controlled her symptoms with a potent topical corticosteroid.<sup>92</sup>

## Conclusion

Vulvar dermatoses are a diverse group of pathology. The vulva can be affected by an inflammatory, infectious, or neoplastic process. Symptomatology is highly variable. The presentation may range from asymptomatic, pruritic, ulcerative, to a chronic disabling condition. The vulva can be a clue to an underlying systemic disease, and careful examination of the anatomic structures is valuable for the treating clinician. Due to the personal nature of symptoms, many patients are hesitant to discuss their symptoms with a healthcare provider. Similarly, some clinicians feel challenged with respect to the management of vulvar diseases. Therefore, it is important that practitioners receive training and gain experience in diagnosing and treating these diseases.

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# Vulvar Vestibulitis Syndrome

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# 62

## Introduction

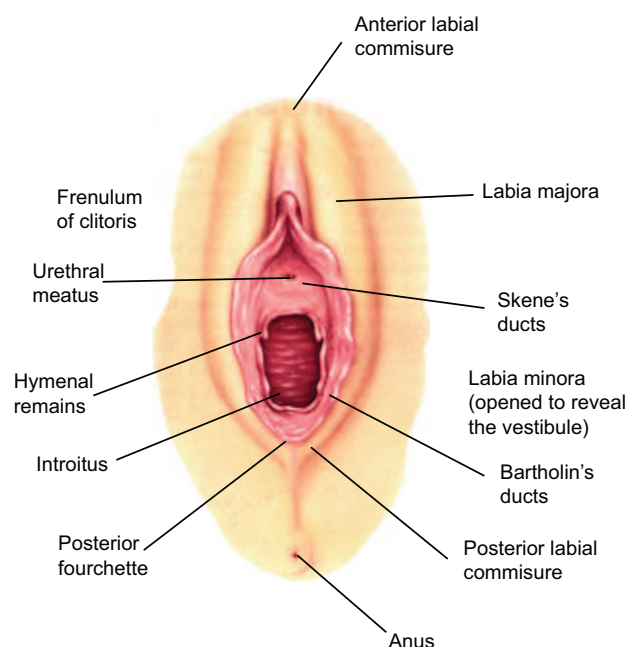
Vulvar vestibulitis syndrome (VVS) is a subset of vulvodynia. VVS is a common but often poorly recognized cause of dyspareunia in premenopausal women. VVS causes severe dyspareunia and thereby affects sexual and reproductive life of predominantly young women. Thus, VVS has a major impact on women's psychological well-being, self-esteem and general quality of life. Unfortunately, VVS largely remains an ignored health problem. Prevalence rates have been poorly studied, but some studies suggest that the rates vary from 9.8%<sup>1</sup> to 15% in general gynecologic practice.<sup>2</sup> In the late 19th century, VVS had already been described in the literature.<sup>3</sup> The etiology or etiopathogenesis is unknown. Although many sexually transmitted viral or bacterial pathogens have been linked to VVS, no evidence supports causative role for any specific micro-organisms. However, the clinical symptoms and signs are straightforward. The diagnosis is based on symptoms such as severe pain on vestibular touch or vaginal entry, tenderness to pressure on the vulvar vestibule, and vulvar erythema of varying degrees.<sup>4</sup> Because the underlying pathophysiology remains unclear, treatment is challenging.

The classification and terminology of vulvodynia has changed during the past few decades starting from the consensus of the International Society for the Study of Vulvovaginal Disease (ISSVD) in 1976 to introduce the term burning vulva syndrome. The latest recommendation provided in 2003 by ISSVD uses the term vulvodynia and classifies subsets on the basis of the site involved. Pain can be generalized or localized when it is restricted only to a limited vulvar area, e.g., vestibule or clitoris. Both generalized and localized pain can be spontaneous or provoked.<sup>5</sup> In the literature the term VVS is widely used for localized provoked vestibulodynia and dysesthetic vulvodynia is used for the generalized spontaneous vulvodynia. These terms are still clinically relevant and useful in clinical practice.

## Vulvar Anatomy

The vulva is the anatomic region between mons pubis in the front and anal orifice in the rear (Fig. 62.1). It includes perineum, labia

majora, labia minora, clitoris and vestibule. The vulvar vestibule may be defined as a ring-like portion of the vulva that extends laterally from the hymenal ring to a line of more keratinized skin on the labia minora, the Hart line. Anteriorly the vestibule reaches upward to the frenulum of the clitoris in the anterior commissure and posteriorly downward to the fourchette and the mucocutaneous Hart line. The vestibule contains urethral meatus, vaginal introitus delineated by the hymen, and vestibular glands. Major vestibular glands are the Skene glands paraurethrally and Bartholin glands with openings adjacent to hymen at 5 o'clock and 7 o'clock. Minor vestibular glands are scattered throughout the vestibulum. Embryologically vestibule differentiates from the urogenital sinus and is thus of endodermal origin, which makes it different from the surrounding vulva which is ectodermal origin. The vestibule is covered with a layer of nonkeratinized stratified squamous epithelium and is richly innervated.



**Fig. 62.1:** Anatomic landmarks of the vulva. Modified from *Modern Colposcopy, Textbook and Atlas* (ref. 7, p. 450).



## Histopathology of Vulvar Vestibulitis

The standard histopathologic examination reveals mild to moderate chronic inflammation with mainly subepithelial lymphocyte infiltrates around minor vestibular glands in patients with vulvar vestibulitis. High numbers of mast cells are present. Increased numbers of nerve bundles and nerve endings beneath and in the vestibular epithelium have been demonstrated by immunohistochemistry.<sup>6</sup>

## Conservative Treatment Modalities

Progress in the treatment of VVS has been unsatisfactory. A wide variety of local and systemic medical, cognitive-behavioral, surgical, and alternative treatment modalities have been proposed and some treatment guidelines have been developed.<sup>7,8</sup> However, these have mostly been based on anecdotal clinical observations and uncontrolled data from case series or case-control studies. Randomized treatment trials are few. Increasing interest has been focused on behavioral and cognitive-behavioral treatments as well as biofeedback with or without electromyographic equipment. This has provided alternative management options. The goal of all management options is to improve psychological adjustments and sexual functioning and thereby reduce pain or increase pain tolerance. Discontinuation of oral contraceptives is often helpful and should be recommended. However, the success rate of conservative treatment modalities has been poor, particularly in severe cases with long history of symptoms. Since 1981, many studies have focused on surgical treatment with encouraging results.

## Surgery

Surgery by vestibulectomy has been considered as “the last resort” in the management of patients not responding to conservative treatment modalities. Several vestibulectomy techniques have been described. However, specific surgical technique as such plays relatively small role in the overall outcome. Overall, surgery by vestibulectomy seems to be surprisingly effective with high success rates.<sup>9</sup> However, lack of randomized trials and insufficient data on complication rates must be emphasized. In 1981, Woodruff et al.<sup>10</sup> reported a case series of patients with dyspareunia treated by perineoplasty operation. Several modifications of the original operation have been reported.<sup>9</sup> In the posterior vestibulectomy operation the excised area includes only the posterior part of vestibule from approximately 10 o'clock to 2 o'clock inside the Hart line. This modification was developed in hope of shorter operation time and less intraoperative and postoperative complications. Also, most women with dyspareunia complain symptoms only in the posterior vestibule.<sup>11</sup> Vestibulectomy always involves vaginal advancement.

Complication rates have not been systematically reported in most vestibulectomy studies. Hemorrhage, hematoma formation, wound infection, and need for resuturation are the most common short-term complications.<sup>9</sup> Because the ducts of the Bartholin glands are invariably transected in vestibulectomy or perineoplasty operations, Bartholin cyst formation from duct occlusion may be inevitable after few months or years, and often requires

operative repair.<sup>12</sup> However, more studies and data on long-term complications of surgical treatment of VVS are needed. In addition to evaluating complication rates more systematically, surgical success should be defined with many different outcome measures, such as improvement of sexual functioning, correction of vestibular tenderness, and overall patient satisfaction. However, operative treatment provides significant relief in dyspareunia in most patients (80% or more in 17 of 33 studies).<sup>9</sup> Better sex life or better sexual functioning has been an additional outcome measure, and improved significantly in all studies.<sup>9</sup> Overall patient satisfaction rates are around 90%.<sup>9</sup> No relief or worsening of dyspareunia is defined as unsuccessful outcome and varies from 0% to 16%.<sup>9</sup>

## Pelvic Floor Muscle Dysfunction and Vaginismus

Pelvic floor muscle dysfunction is often a concomitant problem in patients suffering from vestibulitis and most treatment guidelines recommend biofeedback. Postoperative biofeedback by physical therapy increases the success rate after vestibulectomy. Thus, pelvic floor muscle dysfunction should be recognized. On the other hand, vaginismus patients should always be evaluated for vestibulitis as a possible reason. Strikingly, this was totally ignored in a recent review about the diagnosis and management of vaginismus.<sup>13</sup>

## Psychosexual Aspects

Psychosexual problems challenge the success of any treatment modality. Cognitive-behavioral therapy (CBT) alone has significantly reduced complaints in a large number of patients.<sup>14</sup> If this therapy was combined with surgery, the intervention would be successful in all patients. Although in a randomized study comparing results of vestibulectomy, electromyographic biofeedback, and group cognitive-behavioral therapy, vestibulectomy was superior to other treatment modalities in reducing pain, all three groups improved on psychological adjustment and sexual functioning after 6 months.<sup>15</sup> The treatment gains were maintained or even improved after a follow-up of 2.5 years. In reducing self-reported pain during intercourse, vestibulectomy was no more superior to CBT after longer follow-up.<sup>16</sup>

## Other Aspects

Although surgery is effective in reducing pain, other treatment modalities are also needed to maintain satisfactory outcome. Constant pain has been an exclusion criterion for surgery in many studies. However, the differentiation between VVS, e.g., locally provoked vestibulodynia and unprovoked generalized vulvodynia, e.g., dysesthetic vulvodynia, is not always easy. Some patients certainly have a mixture of both types of the disease and sometimes the tendency for provoked pain is so strong that it is caused even by a minor pressure, for example, from underwear resulting in a false experience of constant pain. When comparing patient characteristics between the groups with successful and unsuccessful results, surgery fails among women who have constant pain in addition to dyspareunia.<sup>17</sup> Patients' willingness to attend psychological evaluation before surgery

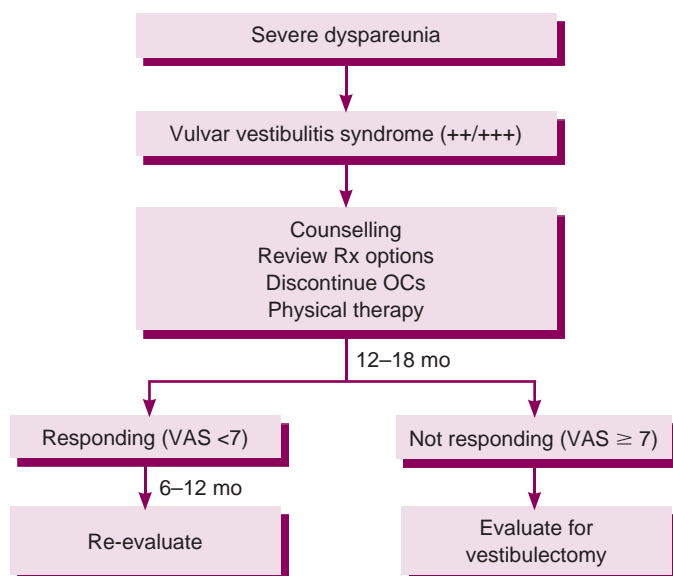
also predicts favorable outcome. Women who understand that the cause of pain is multidimensional are probably more willing to take an active role in rehabilitation efforts after surgery and end up with better outcome.

## Current State of Art

VVS is an important but often ignored cause of severe dyspareunia in young women. Multiple anecdotal conservative treatment modalities have been used with relatively poor success rates. Characteristic clinical criteria for vulvar vestibulitis, uniform symptoms and signs, and long history of severe dyspareunia have been the clinical prerequisites for operative treatment. Surgical treatment has in general been offered to the most severe cases with no response to conservative treatment modalities. Because the definition of successful outcome varies and complications are rarely analyzed, it is somewhat difficult to compare individual studies. One major problem is the lack of randomized studies. Most studies of vestibulectomy report strikingly high success rates and low recurrence rates. We have recently developed an algorithm for evaluation and management of patients with severe VVS, which has proven very useful in clinical practice (Fig. 62.2).

## Conclusions

All chronic pain issues are complex and certainly vulvodynia and vestibulitis represent one of the most challenging chronic pain syndromes. In addition to painful intercourse these women suffer from poor sexual health and poor quality of life. Although surgery improves the pain in most patients, other treatment modalities are often needed in the management. For some patients, conservative modes, e.g., behavioral therapy, sexual counseling, and biofeedback offer relief and improve the quality of life. However, anxious and desperate patients should not be denied the option of surgery.



**Fig. 62.2:** Clinical algorithm for evaluation and management of patients with severe VVS.

## Summary

Vulvar vestibulitis syndrome, a subset of vulvodynia, is a complex pain syndrome. It causes severe dyspareunia and mainly affects young women. The etiology is unknown and no uniformly effective treatment exists. Surgery has been considered as “the last resort” in the management of patients not responding to various conservative treatment modalities. Surgical treatment of vulvar vestibulitis by vestibulectomy has evolved through the years. Surgery is surprisingly effective and provides more satisfaction than any of the conservative treatment modalities available. However, lack of randomized trials of surgery vs. conservative treatment and insufficient data on complication rates associated with surgery must be emphasized.

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# 63

## Male Genital Pain Syndromes

G.A. Luzzi • D. Mandal

### Introduction

Chronic genital and pelvic pain is a relatively common condition of otherwise healthy adult males, and is capable of substantial morbidity. The term 'chronic prostatitis' is often applied in this group of patients, sometimes loosely, and until recently, agreed definitions for prostatitis and pelvic pain syndrome in men have not been available. It is useful to subdivide the major syndromes into acute and chronic bacterial prostatitis (CBP), chronic pelvic pain syndrome (CPPS), and isolated testicular pain syndrome.

### History and Nomenclature

For several decades, it has been recognized that the prostate may be the focus of acute infection, of recurrent infection, and possibly the cause of persistent perineal and penile pain in men. In 1968, Meares et al. reported the development of a 4-glass test to identify prostatic infection and inflammation, and subsequently proposed a classification of prostatitis syndromes based on categorizing chronic prostatitis according to the results of the test.<sup>1,2</sup> Over the subsequent 20 years, a range of terms has been used to denote the various sub-categories of prostatitis, including chronic non-bacterial prostatitis, chronic abacterial prostatitis, and prostatodynia. Criteria for inclusion in these categories, and for the diagnosis of CBP, have varied, making comparisons between published studies difficult and presenting problems in the interpretation of published data on treatment studies and their outcomes. In 1995, the National Institutes of Health (NIH) in the US recommended new definitions and terminology, proposing that chronic non-bacterial prostatitis and prostatodynia should be renamed as CPPS, subdivided into inflammatory and non-inflammatory categories, respectively (Table 63.1).<sup>3</sup> Acute bacterial prostatitis (ABP) denotes acute infection of the prostate; CBP denotes recurrent prostatic infection. CPPS is defined as otherwise unexplained genital or pelvic pain (in or around the penis, perineum, scrotum) lasting for at least 3 months in males of at least 18 years of age. The distinction between inflammatory and non-inflammatory CPPS is based on the finding of white cells in the semen, expressed prostatic secretions (EPS), or in the urine

after prostatic massage. In asymptomatic inflammatory prostatitis, there are no symptoms, but white cells are found in the EPS, semen, or prostatic tissue during evaluation for other disorders.

### Epidemiology

ABP is an uncommon complication of urinary infection, whose exact incidence is unknown. CBP has been reported to represent 5–10% of patients evaluated for prostatitis in hospital-based series.<sup>4,5</sup> However, because diagnostic criteria have varied, this is unlikely to be a reliable estimate. In any case, such estimates can only give a rough idea of the relative incidence of CBP in comparison with other categories of chronic prostatitis (i.e., CPPS) and can tell us little about the incidence of CBP in the general population, which remains unknown. CBP is an uncommon condition, whose frequency may have fallen since the advent of quinolone antibiotics. In contrast, it is clear from hospital-based series and population studies that CPPS is a highly prevalent condition. It accounts for 90–95% of patients in hospital series, and the inflammatory subcategory, based on the finding of white cells in the EPS, was reported to account for around two-thirds of this group. A study of outpatient visits across the US demonstrated that in men aged below 50 years, prostatitis was the most common genitourinary diagnosis made by primary care physicians and urologists.<sup>6</sup> Using a validated chronic prostatitis symptom index developed by a multicenter

**Table 63.1:** NIH Classification of Prostatitis Syndromes<sup>3</sup>

Category	
I	Acute bacterial prostatitis
II	Chronic bacterial prostatitis (CBP)
III	Chronic pelvic pain syndrome (CPPS)
IIIA	CPPS, inflammatory* (formerly, chronic nonbacterial prostatitis)
IIIB	CPPS, non-inflammatory† (formerly, prostatodynia)
IV	Asymptomatic inflammatory prostatitis†

\*Leukocytes in expressed prostatic secretions (EPS), post-prostatic massage urine (urine-3, see Box 63.1), or semen.

†Leukocytes not found in EPS, urine-3, or semen.



collaboration in the US, a survey of nearly 3000 randomly selected Canadian men reported a prevalence of CPPS-type pain in approximately 10% of respondents.<sup>7,8</sup> The response rate was 29%, suggesting a minimum prevalence of 2.8%. Similar prevalences have been suggested by surveys using the same instrument in the US and Singapore (2.3–2.5%).<sup>9,10</sup> On the available evidence, it is reasonable to assume that perhaps 1 in 40 otherwise healthy men experience symptoms suggestive of CPPS at any given time.

## Clinical Features

### ACUTE PROSTATITIS

Acute prostatitis typically presents with the sudden onset of symptoms suggesting acute urinary tract infection (UTI; frequency, urgency, and dysuria) with additional features suggesting prostatic involvement (penile and perineal pain).<sup>11,12</sup> Obstructive urinary symptoms may supervene, including acute urinary retention. Systemic symptoms may be prominent with fever, rigors, and other features of bacteremia. On physical examination, the diagnosis is suggested by the finding of a swollen, tender prostate on digital rectal examination.

### CHRONIC BACTERIAL PROSTATITIS

CBP should be suspected in men with recurrent bacterial UTIs, when the same bacterial organism is isolated from urine cultures on repeated occasions, and in whom a predisposing structural reason for recurrent UTI is not demonstrated on examination by urinary tract imaging. Although patients are frequently symptomless in between recurrences of urinary infection, they may also report symptoms suggesting prostatic involvement, including perineal and penile pain.<sup>11,12</sup>

### CHRONIC PELVIC PAIN SYNDROME

The presence of otherwise unexplained genital or pelvic pain is central to the diagnosis of CPPS. The pain is typically perineal or penile, but may be widely distributed below the belt (Table 63.2). The quality of the pain is highly variable, and may be described as aching, or like a pressure. Sharp or short-lived pain may also be reported, as may dysesthetic features such as burning and tingling. It is useful to consider the pain as part of a characteristic triad in association with urinary and sexual dysfunctions. Urinary dysfunction is usually mild and includes frequency, urgency, feelings of incomplete bladder emptying, and reduced or variable urinary stream. Sexual dysfunction includes pain during or after ejaculation and changes in the color or consistency of the semen. CPPS is occasionally associated with intermittent blood staining of the semen (hematospermia). Erectile dysfunction is reported by a significant minority, 20–40% in published series of men with CPPS.<sup>13,14</sup> Erectile dysfunction in this context is often transitory. On examination, there are frequently no abnormal physical findings. The prostate may be tender to palpation, and prostatic pressure may provoke penile tip pain.

**Table 63.2:** Symptoms of Chronic Pelvic Pain Syndrome<sup>12</sup>

Genital or pelvic pain
Perineal
Penile tip, shaft or base
Testicular
Inguinal
Suprapubic or retropubic
Upper thighs
Rectal
Low back
Urinary dysfunction
Frequency
Urgency
Incomplete bladder emptying
Poor or variable stream
Urethral discharge
Sexual dysfunction
Pain during or after ejaculation
Discoloration of ejaculate
Hematospermia
Erectile dysfunction

The symptoms of CPPS are typically highly variable and usually run a chronic remitting and relapsing course; however, some patients experience constant symptoms and others report intermittent episodes with complete periodic remissions. The potential sickness impact of CPPS is considerable, and was demonstrated in one study to be comparable to that of chronic diseases such as Crohn disease or angina.<sup>15</sup> Patients may report exacerbating factors including posture (e.g., sitting or driving for long periods) and dietary factors (e.g., spicy foods, caffeine, or alcohol). Symptoms frequently persist for months or years. Natural history studies suggest that 40–50% of men with CPPS report improvement in symptoms after one year of follow-up, regardless of treatment.<sup>16,17</sup>

## Pathogenesis

### ACUTE BACTERIAL PROSTATITIS

ABP is most often an uncommon complication of UTI. The prostatic ducts communicate with the prostatic urethra, and therefore infected urine can gain access to the prostate. Consequently, the range of pathogens that cause ABP reflects the spectrum causing urinary infections; these are mostly *Escherichia coli* and other gram-negative rods, which account for more than 80%. *Proteus*, *Klebsiella*, and *Pseudomonas spp.* may all cause ABP.<sup>18</sup> Enterococci, *N. gonorrhoeae*, and anaerobes such as *Bacteroides spp.* may also do so. Rarely, acute prostatitis may arise following bloodborne spread in bacteremic or septicemic illnesses, for instance caused by *Staphylococcus aureus*. ABP may be complicated by the development of a prostatic abscess.<sup>19</sup>

## CHRONIC BACTERIAL PROSTATITIS

In CBP, a nidus of infection becomes established in the prostate and causes relapsing illness. This may follow an acute UTI or episode of ABP, after failure of antibiotic treatment to clear the prostate of infection. The prostate is a deep site which may be relatively inaccessible to certain antimicrobials. CBP may be associated with abnormalities of the prostatic architecture, including fibrosis, microabscess formation, and the presence of prostatic calculi or calcification. The incidental finding of prostatic calculi or calcification is very common in older men.<sup>20</sup> Prostatic calculi may form a source for recurrent bacteriuria.<sup>21</sup> The range of organisms that cause CBP, like ABP, is similar to those causing UTIs and therefore gram-negative rods, especially *E. coli*, are the commonest pathogens.<sup>22</sup> Enterococci may also be responsible. The role of gram-positive cocci is controversial. Ultrastructural studies in antibiotic-refractory CBP have demonstrated persistence of gram-positive cocci in prostatic tissue, in the form of polysaccharide-coated microcolonies.<sup>23</sup> These patients may not have a history of recurrent bacteriuria and the significance of the histological findings is debatable. In CBP, a range of prostatic fluid changes have been described, including a rise in pH and depletion of some components including zinc and a prostatic antibacterial factor.<sup>24</sup> Although zinc treatment was proposed on the basis of these findings, oral supplementation with zinc does not alter prostatic zinc levels and there is no evidence for benefit. Fungal infections may cause chronic prostatitis, especially in the immunosuppressed patients (such as patients with advanced HIV infection).<sup>25,26</sup>

## CHRONIC PELVIC PAIN SYNDROME

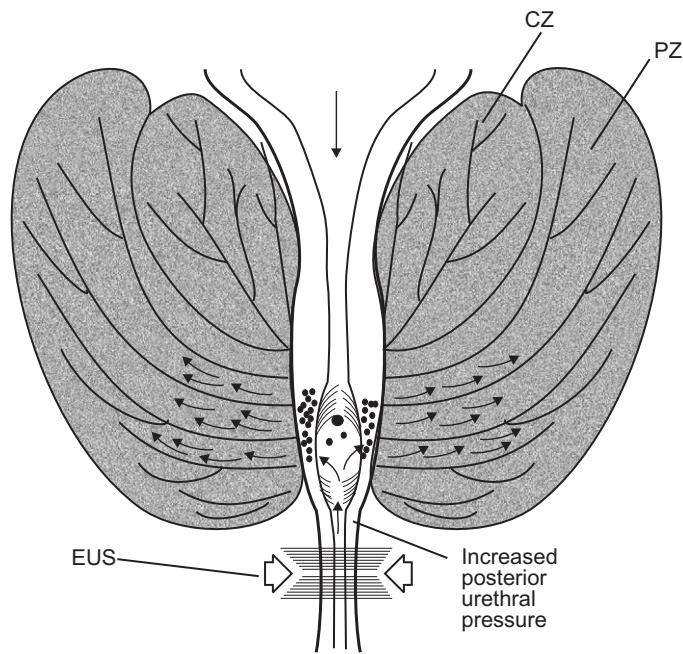
The cause of the much commoner CPPS remains unknown despite 20 years of investigation. White cells may be detected in the EPS of the majority of men with CPPS, with a predominance of polymorphs, and a smaller proportion of macrophages (which may be lipid laden) on Gram staining. Immunocytological analysis of the cells obtained after prostatic massage in men with inflammatory CPPS has shown that the spectrum is made up of mostly granulocytes (82%), with macrophages (11%), and also small numbers of T-lymphocytes (5%) and B-lymphocytes (2%).<sup>27</sup> The cause of the inflammatory response is not known, and understandably, its presence has stimulated a search for occult infection. Although some research groups have reported detection of *Chlamydia trachomatis* or *Ureaplasma urealyticum*, these findings have not been reproduced in other detailed studies and the balance of evidence would suggest that they are not significant causes of CPPS.<sup>28,29</sup> Using molecular detection techniques on prostatic tissue in men with inflammatory CPPS, the presence of DNA sequences common to a range of bacteria was reported in 1996.<sup>30</sup> In this study, which included men with inflammatory CPPS and without urethritis, only 4 of the 135 (3%) had *C. trachomatis* DNA detectable by polymerase chain reaction in prostatic tissue obtained by transperineal biopsy. *Ureaplasma* was not detected. The bacterial sequences that were commonly

found related to unusual organisms that did not represent possible contamination by skin or fecal commensals. Although the findings suggest a possible etiology implicating unusual, non-culturable bacteria, their significance is uncertain because similar DNA sequences have been detected in men without inflammatory CPPS, for instance in prostate tissue derived from men who underwent prostatectomy for prostate cancer.<sup>31</sup>

Although the cause of the inflammatory reaction in CPPS remains unknown, a central role for the inflammatory response in this condition is supported by the finding of elevations in certain pro-inflammatory and anti-inflammatory cytokines. Several investigators have reported similar results, with elevations in interleukin-1b and TNF-alpha in EPS and semen, and tissue markers of cellular activation in prostatic biopsies.<sup>32–34</sup> Interleukin-6, interleukin-8, and interleukin-10 have also recently been reported to be elevated.<sup>35,36</sup> Some of these cytokines are thought to have an anti-inflammatory role, and their elevation implies production to counterbalance the effects of the pro-inflammatory mediators. It is noteworthy that these elevations have been detected not only in men with inflammatory CPPS but also in those with no white cells detectable in the EPS, although at a lower level.<sup>32,33</sup> This suggests a common pathogenesis for inflammatory and non-inflammatory CPPS, and undermines the value of making a distinction between the two entities, which have the same clinical symptomatology. Moreover, whereas white cells do not correlate with presence or severity of symptoms,<sup>37</sup> it has been reported that cytokine levels in CPPS may correlate with symptom severity.<sup>37,38</sup>

Animal models, using mice or rats, were developed for the study of bacterial and non-bacterial prostatitis.<sup>39,40</sup> C57bl/6 mice develop an autoimmune prostatitis when injected with homogenized mouse prostate, raising the question of whether the inflammatory response in CPPS may be an autoimmune phenomenon.<sup>40</sup> Evidence to support this hypothesis in humans is limited to one small study, and more work is needed before conclusions can be drawn.<sup>41</sup>

Urodynamic studies have suggested a possible neuromuscular origin for CPPS. Abnormal contraction or spasm at the external urethral sphincter may be detectable during voiding, and it has been proposed that the consequent rise in prostatic urethral pressures might provoke prostatic pain (Fig. 63.1).<sup>42–44</sup> Secondary reflux of urine into the prostatic parenchyma might provoke a chemical prostatitis, simulating an inflammatory response. Intraprostatic reflux of urine can be demonstrated in men with inflammatory CPPS, following installation of carbon particles into the bladder.<sup>45</sup> Moreover, prostatic calculi have been shown to be composed of constituents of urine rather than prostatic secretions, implying that such reflux may occur commonly. Functional obstruction at the bladder neck, as proposed by this hypothesis, could explain the subjective reports of flow abnormalities that may be confirmed on uroflowmetry in some patients with CPPS. Neuromuscular abnormalities of this type might be triggered by a range of factors, including urinary or genital infections and other painful processes including surgery and trauma.



**Fig. 63.1:** Possible neuromuscular mechanism for chronic pelvic pain syndrome. Increased tension at the external urethral sphincter (EUS, where pelvic floor meets membranous urethra) causes a rise in prostatic urethral pressure and reflux of urine into prostatic parenchyma, preferentially into peripheral zone (PZ).<sup>42</sup> CZ indicates central zone.

Psychological factors may also be important in the genesis and perpetuation of symptoms in men with CPPS. Studies have demonstrated higher scores than control groups for depression, anxiety, somatization, and hypochondriasis.<sup>46</sup> CPPS has similarities to other regional chronic pain syndromes.<sup>47</sup> It has been proposed that the inflammation detectable in this condition may be neurogenic in origin, caused by release of neuropeptides such as substance P.<sup>49</sup>

## Diagnosis

### ACUTE BACTERIAL PROSTATITIS

The diagnosis of ABP should be suspected in men presenting with symptoms of acute UTI, when perineal or penile pain and obstructive symptoms are present. The finding of a swollen, tender prostate on rectal examination is sufficient to confirm the diagnosis. Imaging by transrectal ultrasound (TRUS) or computed tomographic scan can provide further confirmation. Urine dipstick testing indicates the presence of urinary infection (leukocytes, nitrite, red cells, and protein) and, before antimicrobials are started, urine cultures will usually help identify the responsible organism. Blood cultures may also prove positive. After an episode of ABP, the urinary tract should be investigated by ultrasonography or intravenous urography to exclude a structural predisposing factor for UTI.

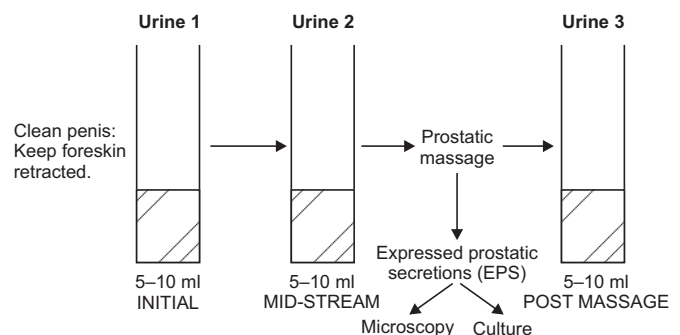
### CHRONIC BACTERIAL PROSTATITIS

The diagnosis of CBP should be suspected in men with recurrent UTI caused by the same organism, when urinary tract imaging does not demonstrate a predisposing cause. TRUS may demonstrate abnormalities of the prostatic parenchyma or the presence of calculi. Prostatic calcification or calculi may also be evident on urography, but these may be also detected in the absence of prostatitis. The 4-glass test may be helpful to confirm CBP (Fig. 63.2). The test should not be performed in the presence of UTI or, ideally, within one week of antibiotic treatment. The aim of the investigation is to examine the EPS, obtainable in approximately 70% of examinations, by microscopy and culture. When EPS are not obtainable, the test relies on quantitative microscopy (for white cells) and culture (colony-forming units) of the urine voided immediately after prostatic massage (urine-3), in comparison with the mid-stream urine (urine-2). In theory, EPS culture should produce a significant growth of the organism responsible for recurrent UTIs, providing confirmation of the presence of a prostatic focus. In practice, even when there is strong clinical suspicion of CBP on the basis of recurrent UTIs, the organism may not be identified by the 4-glass test. The reliability of the test in the diagnosis of CBP has not been determined, and in instances where the test does not provide confirmation of CBP, a therapeutic trial is usually indicated regardless of the results.

### CHRONIC PELVIC PAIN SYNDROME

The diagnosis of CPPS is a clinical one, and because the etiology of the condition is not known, a confirmatory diagnostic test has not been developed. A number of potential investigations have been proposed. McNaughton-Collins conducted a systematic review of candidate diagnostic tests for CPPS, and examined critically those who had been evaluated in control studies.<sup>50</sup> She concluded that no diagnostic test has been identified that is sufficiently validated for use in clinical practice, not even the 4-glass test. This conclusion remains current.

Traditionally, the 4-glass test has been used to investigate suspected prostatitis (see Box 63.1 and Fig. 63.2). The finding of a significant number of white cells in the EPS ( $>1000/\text{mm}^3$  or  $>10/\text{high power field}$ , magnification  $\times 400$ ) has been used



**Fig. 63.2:** The 4-glass test (see Box 63.1).



**Box 63.1** The 4-Glass Test\* (See Fig. 63.2)

Advise patient to hold urine for 2 hours and not to ejaculate for at least 2 days.

No antibiotic for at least 1 week.

**Procedure**

1. Clean end penis with sterile saline or water.
2. Collect first void 5–10 mL (urine-1).
3. Collect mid-stream 5–10 mL (urine-2).
4. Prostatic massage for 1 minute (collect EPS<sup>†</sup>).
5. Clean penis (as for 1).
6. Collect next 5–10 mL and empty bladder (urine-3).

\*EPS indicates expressed prostatic secretions. One drop on slide for immediate microscopy. If sufficient, also send for culture.

Interpretation (See Table 63.1)

Diagnosis	EPS		Urine-3	
	WBC	Culture	WBC	Culture
CBP	+	+	+	+
CPPS, inflammatory	+	-	+	-
CPPS, non-inflammatory	-	-	-	-

<sup>†</sup>>1000 cells/mm<sup>3</sup> or ≥10 cells/hpf (high power field, x400).

<sup>§</sup>WBC in urine-3 minus urine-2 ≥10 cells/hpf.

<sup>\*\*</sup>Quantitative counts; ratio of urine-3/urine-2 ≥10.

\*Modified after Meares & Stamey,<sup>1</sup> Leigh,<sup>22</sup> Schiefer et al.<sup>49</sup> Thin 1997.<sup>63</sup>

as useful confirmation for suspected prostatitis. However, the detection of white cells does not correlate with symptoms, and an asymptomatic inflammatory prostatitis is also known to occur. The significance of asymptomatic prostatic inflammation is not known. If EPS are not obtained, a rise in urinary white cells after prostatic massage has been used as evidence for prostatic inflammation. However, this has not been standardized. Nickel developed a 2-glass technique as a simplified version of the 4-glass test and reported comparable results.<sup>51</sup>

The reliability of the 4-glass test in detecting the presence of prostatic inflammation is not known, because it has not been compared against an independent standard. This means that its positive and negative predictive values are not known. Moreover, the distinction between inflammatory and non-inflammatory CPPS has not been shown to influence clinical management or prognosis. Clinical practice surveys have shown wide variation in use of the 4-glass test in the investigation of CPPS. A survey of urologists in the US revealed that only a small minority request the investigation (80% responded never or rarely).<sup>52</sup> A survey of genitourinary medicine physicians in the UK demonstrated that although the diagnosis of CPPS was frequently made, the 4-glass test was routinely used by only one-third for investigating the condition.<sup>53</sup> Some authors have recommended that the test should be confined to research protocols.<sup>54,55</sup> In the light of findings on cytokine changes that are detectable in both inflammatory and non-inflammatory CPPS, it is debatable whether the 4-glass test provides any useful information in the context of CPPS.

**Differential Diagnosis of CPPS**

In the absence of a reliable confirmatory investigation, CPPS remains a clinical diagnosis that relies on the exclusion of other

**Table 63.3:** Differential Diagnosis of Chronic Pelvic Pain Syndrome (CPPS)

Bladder conditions
Carcinoma in situ or carcinoma <sup>56</sup>
Interstitial cystitis <sup>57</sup>
Bladder outlet obstruction <sup>58</sup>
Bladder irritation by colonic carcinoma or diverticulitis
Seminal vesicle abnormalities
Seminal vesicle calculi <sup>59</sup>
Seminal vesicle cysts (e.g., associated with ipsilateral renal agenesis) <sup>60</sup>
Miscellaneous
Occult inguinal and femoral hernias
Inguinal ligament enthesopathy <sup>61</sup>
Lumbosacral arthropathy
Recurrent genital herpes simplex <sup>62</sup>

potential causes for symptoms. The definition proposed by the NIH recommends exclusion of genital infections including *Chlamydia* and herpes simplex, UTI, bladder neoplasia including carcinoma in situ, urinary tract stone disease, and neurological causes for symptoms.<sup>3</sup> For clinical purposes, a differential diagnosis for CPPS is shown in Table 63.3. In excluding other causes for symptoms, a urine dipstick test should always be performed and significant urine abnormalities, in particular microscopic hematuria, should not be attributed to CPPS. The presence of irritant-type voiding symptoms should be investigated by cystoscopy to exclude bladder carcinoma, carcinoma in situ, and interstitial cystitis.<sup>56,57</sup> Obstructive urinary symptoms with a flattened trace on uroflowmetry should be investigated by cystoscopy to exclude bladder outlet obstruction and urethral stricture.<sup>58</sup> Although TRUS has been recommended as a diagnostic test for CPPS, changes in the prostatic parenchyma that are frequently identified are relatively non-specific and the test cannot be used to confirm the diagnosis.<sup>50</sup> TRUS may identify prostatic cysts that may be amenable to drainage.<sup>63</sup> Urinary tract imaging, for instance by ultrasonography, will rarely detect a relevant structural abnormality. The presence of a significant residual bladder volume on ultrasound should lead to further investigation to exclude bladder outlet obstruction.<sup>58</sup> If renal agenesis is identified, this should raise the possibility of ipsilateral seminal vesicle abnormalities, including cystic changes, which can predispose to recurrent pelvic pain and may be amenable to drainage or excision.<sup>60</sup>

**Management****ACUTE BACTERIAL PROSTATITIS**

Patients with ABP require urgent treatment with an antibiotic regimen that is likely to cover uropathogens while waiting for culture and sensitivity results. Rest and adequate hydration should be recommended and analgesia prescribed as necessary. Although controlled trials are not available to guide antibiotic

selection or duration of treatment, penetration of antibiotics into the acutely inflamed prostate is likely to be good, and in mild episodes, oral treatment with co-amoxiclav (amoxicillin + clavulanic acid) or a quinolone such as ciprofloxacin may be sufficient. The antibiotic may need to be changed in the light of culture and sensitivity results. Patients with severe systemic features and those whose condition does not respond rapidly to oral treatment, may need admission to hospital for intravenous antibiotics. In general, a prolonged course of treatment is recommended, for instance 4 weeks, with the aim of reducing the risk of subsequent CBP.<sup>11,18</sup>

Acute retention of urine is an occasional complication of ABP, and should be managed by suprapubic catheterization. Urethral catheterization should be avoided because of the risk of damage to the swollen prostate. Prostatic abscess is a rare but serious complication of ABP, requiring drainage by transurethral or perineal routes.<sup>19</sup>

### CHRONIC BACTERIAL PROSTATITIS

In the pre-quinolone era, CBP had a reputation for persistence despite prolonged courses of antibiotics. Antibiotic penetration across the prostate-blood barrier was thought to be a factor. Observational studies suggested eradication rates of only 30–40% for co-trimoxazole, after 3-month treatment.<sup>64</sup> The sulfonamide component of co-trimoxazole does not penetrate well into the prostate and trimethoprim may, therefore, be equally effective. The advent of quinolone antibiotics revolutionized the treatment of CBP. However, only a few controlled trials of oral antibiotic treatment of CBP have been published. In 5 studies evaluating quinolones in CBP involving a total of 121 patients, the reported non-recurrence rates were 82% at one month after treatment, and 64% at 6 months after treatment (using courses of 2–7 weeks duration).<sup>65–68</sup> These and observational reports suggest that initial therapy for CBP with 4 weeks of a quinolone is reasonable, assuming a sensitive organism. Ciprofloxacin, 500 mg twice daily or ofloxacin 200–400 mg twice daily is a suitable choice. CBP that recurs despite treatment is fortunately rare, and management is difficult. Options include using longer courses of quinolone, such as 5 months, or a combined medical and surgical approach.<sup>69,70</sup>

### CHRONIC PELVIC PAIN SYNDROME

The management of CPPS is generally unsatisfactory, in that no reliably effective treatments have been identified.<sup>12,65</sup> Numerous candidate treatments have been reported, mostly in uncontrolled studies. Caution is required in interpreting the results of such studies, because benefit in the placebo arms of blinded, controlled trials has been as high as 30%.<sup>71</sup> Therefore, response rates at this level in uncontrolled studies may not indicate a genuine treatment effect.

The NIH chronic prostatitis symptom index is a widely adopted questionnaire about symptoms which can be useful in monitoring symptom severity and impact over time and after trials of treatment.<sup>7</sup>

**Table 63.4:** Management of Chronic Pelvic Pain Syndrome\*

Explanation, reassurance
Use diagrams and written information
General measures
Fluids
Regular ejaculation <sup>72</sup>
Hot baths
Avoid activities that provoke symptoms
Dietary modification (individual cases)
Antibiotics
Doxycycline, <sup>73</sup> minocycline <sup>73,74</sup>
Erythromycin <sup>76</sup>
Ofloxacin <sup>77</sup>
Anti-inflammatory agents
Ibuprofen, diclofenac
Alpha blockers
Alfuzosin, <sup>78</sup> tamsulosin <sup>79</sup>
Terazosin <sup>79,80</sup>
Low-dose antidepressants
Amitriptyline 10–50 mg nocte
Anticonvulsants
Gabapentin <sup>81</sup>
Miscellaneous
Transurethral or transrectal
Microwave thermotherapy <sup>82,83</sup>
Pollen extract <sup>84</sup>
Allopurinol <sup>85,86</sup>
Finasteride <sup>87</sup>
Quercetin <sup>88</sup>

\*Adapted from Luzzi G.<sup>12</sup>

A range of candidate treatments that have been proposed or evaluated for CPPS is shown in Table 63.4. In her systematic review for the Cochrane collaboration, McNaughton-Collins examined published randomized or controlled trials and identified 14 that met the inclusion criteria.<sup>50</sup> Quantitative analysis was prevented by variations in study design and interventions used. This critical examination of reported treatments for CPPS concluded that no treatment approach is currently supported by good evidence. Despite the lack of supporting evidence for benefit, antibiotics are frequently used as first-line treatment for CPPS. If antibiotics are used for CPPS, it is logical to select agents with broad-spectrum activity and good prostatic penetration, such as doxycycline, ofloxacin, and erythromycin. A proportion of patients seem to benefit, and this may relate to the non-antibiotic properties of some of these agents. For instance, tetracyclines are known to have anti-inflammatory effects, and quinolones may influence cytokine pathways.<sup>89</sup> However, the evidence does not support prolonged use of antibiotic treatment for CPPS.

Early small, controlled, and observational studies of alpha blockers in CPPS showed variable results, with apparent benefit in a proportion of men.<sup>50,78,79</sup> Alpha blockers may act in CPPS by relaxing smooth muscle at the bladder outlet, and may therefore be particularly helpful in men reporting flow abnormalities and prominent urinary symptoms including frequency and nocturia. Alfuzosin and tamsulosin have been considered to be reasonable choices to try in men with persistent symptoms. Unfortunately, more recent controlled studies of alpha blockers in CPPS have not confirmed clinical benefit and their role in the management of CPPS has become uncertain.<sup>90,91</sup>

Transurethral microwave thermotherapy and treatment with allopurinol were reported to be effective in small, controlled trials, but have not been widely adopted.<sup>83,84</sup> Other treatments reported to help some patients in observational studies or anecdotally include pollen extract, repetitive prostatic massage, acupuncture, and oral corticosteroid. However, the available evidence does not justify recommending their use.<sup>85,92</sup>

Finasteride is a 5 alpha-reductase inhibitor that reduces prostate size; 5 mg daily was reported to improve prostatitis symptom scores in comparison with placebo in 41 men with inflammatory CPPS, after a 12-month treatment period. However, pain scores did not show significant reduction.<sup>87</sup> Quercetin, a naturally occurring bioflavonoid with known anti-inflammatory and anti-oxidant properties, was reported to produce a significant reduction in NIH symptom scores, in a coformulation with bromelain and papain. After one month, two-thirds of men reported benefit in comparison with 20% in the placebo group.<sup>88</sup> This was a well-designed study, but long-term outcome data are not available, and the results need to be confirmed in a larger trial before conclusions can be drawn.

Pain management approaches have been underevaluated in CPPS. Treatments that are well-established in other chronic pain syndromes include low-dose tricyclic antidepressants and the anticonvulsant gabapentin.<sup>81</sup> These are occasionally used in CPPS and deserve systematic evaluation, as do psychological approaches including cognitive behavioral therapy.

In practice, many patients with mild symptoms of CPPS respond to reassurance and an explanation of why their symptoms arise, using diagrams and a leaflet to take away. Simple measures that may be helpful include regular ejaculation and hot sitz baths. In individual cases, avoidance of provoking physical or dietary factors may be appropriate; these are highly variable and may include cycling, caffeine, and alcohol. The response to simple analgesics and non-steroidal, anti-inflammatory drugs is often disappointing. A 2- to 4-week course of doxycycline, ofloxacin, or erythromycin may be tried. Patients with severe persistent symptoms present a difficult management problem that may seem intractable, with associated psychological factors. A trial of alpha blocker or low-dose tricyclic antidepressant may be considered. Coexistent depression should be evaluated and treated appropriately, and referral for specialist assessment of this may be justified. Patients with significant chronic symptoms may derive support from sharing their experience with other prostatitis/CPPS sufferers via the internet.

## Prognosis of Chronic Pelvic Pain Syndrome

Although effective treatment has not been identified, patients can be advised that there is a reasonable likelihood that they will experience amelioration of symptoms over time. In recently diagnosed CPPS, most men experience some improvement in symptoms over the subsequent 6 months.<sup>93</sup> In the largest natural history study of men with CPPS, one-third showed moderate or marked improvement over 2 years.<sup>94</sup>

## Isolated Testicular Pain

Although testicular pain can be a feature of CPPS, chronic pain confined to one or both testicles is usually regarded as a distinct entity and there may be some practical value in considering isolated testicular pain separately. Chronic testicular pain, defined as pain present for more than 3 months, is not a rare condition, yet surprisingly few series have been reported in the medical literature. The range of causes was considered in a series of 43 patients (Table 63.5): at least quarter had no identifiable cause.<sup>95,96</sup> This proportion is likely to be higher in non-surgical settings. The relationship between acute epididymitis and subsequent chronic testicular pain has not been studied systematically and in this series, 35% of men with chronic testicular pain had a history of previous epididymitis. Chronic pain may also follow vasectomy. Chronic pain lasting more than 3 months has been reported in up to 5% of men after this procedure.<sup>97</sup>

The pathogenesis of chronic testicular pain is not understood. Histological examination of epididymectomy and orchidectomy specimens following surgery for chronic pain reveals abnormalities in only a small minority. These are mostly chronic, non-specific, inflammatory changes, and testicular tubular atrophy that may be an incidental finding.<sup>96</sup> The features that suggest a regional chronic pain syndrome include the lack of abnormal physical findings or abnormalities on investigation, and a history of multiple, unsuccessful treatments. As in other chronic pain syndromes, the condition may follow an initiating or trigger event, such as an infection, a surgical procedure, or an episode of trauma. Subsequently, factors that promote the maintenance of pain include biological factors such as nerve damage, upregulation of pain circuits, and psychological factors including personality type and depression.

In the management of chronic testicular pain, there are no controlled trials to assist decision making. Conventional

**Table 63.5:** Causes of Isolated Chronic Testicular Pain in a Series of 43 Patients<sup>95</sup>

	(%)
Previous epididymitis	35
Previous surgery	21
Previous trauma	14
Unknown (idiopathic)	23
Other <sup>a</sup>	7

<sup>a</sup>Varicocele, hydrocele, and testis tumor.



analgesics and anti-inflammatory agents are often unhelpful. As for other chronic pain syndromes, a trial of low-dose tricyclic antidepressant, such as amitriptyline, may be considered. Spermatic cord block using a mixture of local anesthetic and steroid may relieve pain, but the effect is usually transient.<sup>98</sup> The procedure can help identify the subgroup of men who are likely to respond to more destructive approaches, such as nerve stripping or microsurgical denervation of the spermatic cord.<sup>97–99</sup> However these specialized techniques are not widely available, and are associated with some risk of testicular atrophy if the testicular artery is damaged. In postvasectomy pain, reversal of vasectomy (vasovasostomy) may be considered but its effectiveness is unclear from the literature, and men may be reluctant to undergo the procedure.<sup>96</sup> Epididymectomy or orchidectomy is sometimes considered for intractable testicular pain. However, it has been reported that epididymectomy is often ineffective and should be avoided.<sup>96</sup> Orchidectomy may be considered as a last resort, but even this may not abolish the pain and some authors advise avoidance<sup>100</sup>; this might possibly be explained in some cases by misdiagnosis, in men who report testicular pain in the context of CPPS. The anticonvulsant gabapentin, which has been reported to help some patients with chronic testicular pain in a small observational series,<sup>81</sup> and psychological approaches including cognitive behavioral therapy, deserve systematic evaluation.

## Conclusion

Chronic genital and pelvic pain is a relatively common condition of otherwise healthy adult males, and is capable of substantial morbidity. It is useful to subdivide the major syndromes related to chronic genital and pelvic pain in men into ABP and CBP, CPPS, and isolated testicular pain syndrome. While symptoms of CPPS are typically highly variable and usually run a chronic remitting and relapsing course, the cause of CPPS remains unknown despite 20 years of investigation. A central role for the inflammatory response in this condition is supported by the finding of elevations in certain pro-inflammatory and anti-inflammatory cytokines. Urodynamic studies have suggested a possible neuromuscular origin for CPPS. Psychological factors may also be important in the genesis and perpetuation of symptoms in men with CPPS. In the absence of a reliable confirmatory investigation, CPPS remains a clinical diagnosis that relies on the exclusion of other potential causes for symptoms. The management of CPPS is generally unsatisfactory, in that no reliably effective treatments have been identified; however, symptoms improve in a substantial proportion of men over a timescale of 6 months to 2 years.

ABP is most often an uncommon complication of UTI. The finding of a swollen, tender prostate on rectal examination is sufficient to confirm the diagnosis, and patients require urgent treatment with an antibiotic regimen that is likely to cover uropathogens.

In CBP, a nidus of infection becomes established in the prostate and causes relapsing illness. This may follow an acute UTI or episode of ABP, after failure of antibiotic treatment to clear the prostate of infection. The diagnosis of CBP should be suspected

in men with recurrent UTI caused by the same organism, when urinary tract imaging does not demonstrate a predisposing cause. The advent of quinolone antibiotics revolutionized the treatment of CBP and recurrence after treatment is fortunately uncommon.

Although testicular pain can be a feature of CPPS, chronic pain confined to one or both testicles is usually regarded as a distinct entity. The pathogenesis of chronic testicular pain is poorly understood and the management remains unsatisfactory.

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# section **xi**

## **SEXUALLY TRANSMITTED SYNDROMES AND OTHER ORGAN SYSTEMS**

— *Jonathan Ross*

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# 64

## Ocular Manifestations of Sexually Transmitted Infections

Jyotirmay Biswas • Parthopratiim Dutta Majumder  
• Sudharshan S.

### Introduction

The World Health Organization estimates that 480 million new cases of sexually transmitted diseases (STDs) have occurred throughout the world in the year 2005 in men and women aged 15–49 years.<sup>1</sup> Despite stepped-up public awareness campaigns in recent years regarding the hazards of unprotected sexual intercourse, sexually transmitted diseases continue to exact a troubling toll on our society. Many of these conditions commonly affect the eye, and thus pose a critical concern for primary care. The ophthalmologist can even be the initial clinician who identifies the systemic condition, as patients may often seek advice when vision is impaired. This chapter provides an overview of ocular lesions in various sexually transmitted infections. Common sexually transmitted infections, which may cause ophthalmic lesions, are enumerated in Table 64.1.

### Syphilis

Syphilis is a systemic infection caused by a spirochete, *Treponema pallidum*, which can produce multiple ocular inflammatory and structural changes. The first clear clinical description of syphilis was published during the Renaissance, when the disease spread across Europe. At that time syphilis was termed as the “great pox” to distinguish it from small pox. The ocular manifestations of syphilis, singly and as a coinfection with HIV, are summarized below.

**Table 64.1:** Common Sexually Transmitted Diseases Causing Ocular Lesions

- |      |  |
|------|--|
| I.   | Syphilis                               |
| II.  | <i>Neisseria gonorrhoeae</i> infection |
| III. | Chlamydia trachomatis infection        |
| IV.  | Genital herpes                         |
| V.   | Crab louse infestation                 |
| VI.  | Human immunodeficiency virus infection |

### OCULAR LESIONS IN THE VARIOUS CLINICAL STAGES OF SYPHILIS

#### Primary Syphilis

The first clinical sign of syphilis is the chancre, which generally occurs in the area of invasion by *Treponema pallidum* usually 3 weeks after exposure. Extragenital chancres may be seen on the lip, tongue, tonsil, nipple, finger, and anus. Primary lesions are rarely found on the eyelids or conjunctiva.<sup>2</sup> Other ocular signs in the primary stage include conjunctivitis and blepharitis.

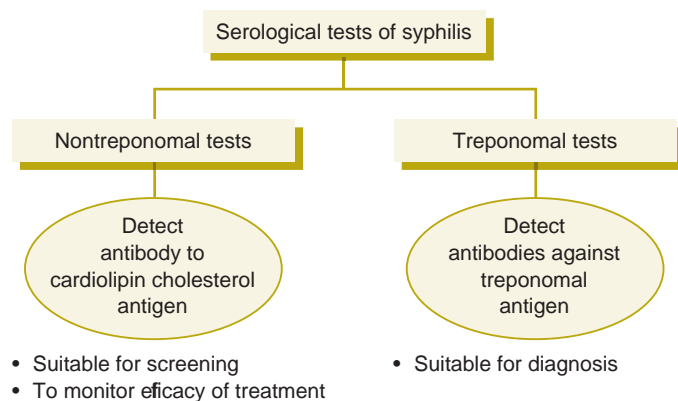
#### Secondary Syphilis

Three weeks to 6 months after the primary infection with *Treponema pallidum*, hematogenous dissemination of the organism may be associated with the signs and symptoms of secondary syphilis. Ocular involvement is strongly suggestive of the involvement of the central nervous system (CNS) and may be considered as synonymous with neurosyphilis.<sup>3–5</sup> Secondary syphilis is characterized by a painless maculopapular skin rash, and although the face is spared, sometimes the eyelids may be affected. Hair follicle involvement may lead to temporary loss of the outer half of the eyebrows or eyelashes and patchy loss of hair on the face and scalp. Anterior uveitis, manifesting as a mild acute iritis is the most common ocular manifestation of this stage and occurs in about 5% of untreated cases,<sup>6</sup> but seldom before the sixth month of infection. The other eye is affected in nearly one-half of the patients. Diffuse and nodular scleritis (Figs. 64.1 and 64.2) can manifest in secondary syphilis. Choroiditis with vitritis can also develop during the late secondary stage and lead to focal chorioretinal atrophy. Central nervous system involvement with its ocular manifestations may be found in about one-fourth of the patients with secondary syphilis (see below).<sup>3,7,8</sup>

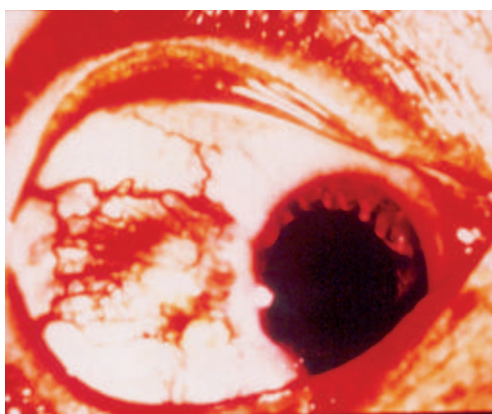
#### Tertiary Syphilis

About one-third of the patients develop the clinical signs of obliterative endarteritis in late syphilis, usually many years after the





**Fig. 64.1:** Serological tests used for diagnosis of syphilis.



**Fig. 64.2:** Diffuse scleritis in syphilis.

onset of disease. Ocular signs have been noted in approximately 10% of patients with tertiary syphilis. Pupillary abnormalities are among the most common ocular manifestations (Table 64.2).<sup>9,10</sup>

**Gummas:** Gummas are necrotic, granulomatous lesions produced by focal obliterative endarteritis. They may involve any organ including the eye. In the eye, gummatous lesions are commonly found in the lacrimal structures, orbit, and optic nerves. Gummas on the cornea and sclera have been reported.<sup>11–14</sup>

**Cardiovascular syphilis and the eye:** Eye involvement in patients with cardiovascular syphilis occurs as a result of syphilitic vasculitis. The common ocular features of syphilitic vasculitis include scleritis, chronic iridocyclitis, choroiditis, and retinal vasculitis with periarteriolar sheathing.

## NEURO-OPHTHALMIC FEATURES

### Optic Nerve

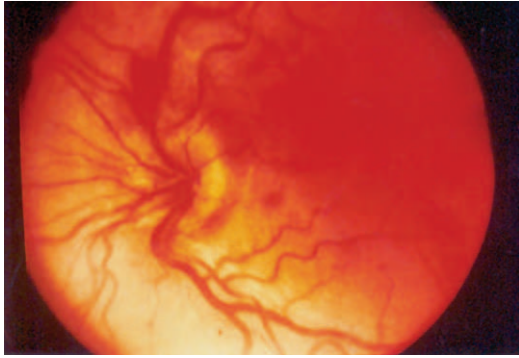
The optic nerve is affected in a substantial proportion of patients with secondary syphilis or tertiary syphilis.

- Optic perineuritis is an inflammation of the meningeal sheaths of the optic nerve that produces a mild swelling of the optic disc but does not adversely affect visual acuity, color vision, or the visual field.<sup>15</sup>

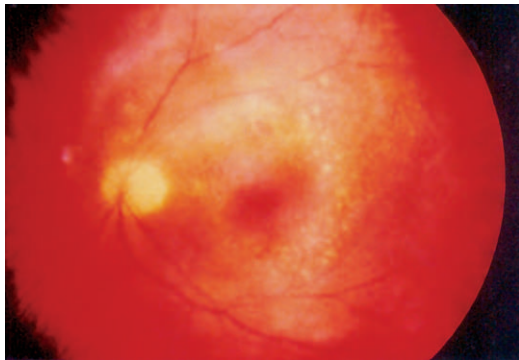
**Table 64.2:** Structure-wise Involvement of the Eye in Syphilis

Ocular structure	Type of lesion/ involvement
<b>Eyelid</b>	Chancre Gumma Tarsitis Ulcerative blepharitis
<b>Conjunctiva</b>	Chancre Granuloma Tarsitis
<b>Orbit</b>	Periostitis Gumma (extraocular muscle, lacrimal gland or within orbit)
<b>Cornea</b>	Interstitial keratitis Ulcers Deep punctate keratitis Keratitis profunda Keratitis punctate profunda Keratitis pustuliformis profunda Keratitis linearis migrans
<b>Sclera</b>	Episcleritis Scleritis (nodular or diffuse; anterior or posterior) Gumma
<b>Iris and ciliary body</b>	Roseola Papules Gumma
<b>Pupil</b>	Light- near dissociation (A-R pupil)
<b>Lens</b>	Capsular rupture and necrotizing cortical inflammation Traumatic dislocation
<b>Glaucoma</b>	Secondary to uveitis (late manifestation)
<b>Optic nerve</b>	Perineuritis Anterior optic neuritis Retrobulbar neuritis Neuroretinitis Papilledema Optic atrophy
<b>Motility Dysfunctions</b>	Oculomotor, abducens, trochlear associated paresis Basilar meningitis Periodic alternating nystagmus
<b>Retina and vitreous</b>	Chorioretinitis—pseudoretinitis pigmentosa, salt and pepper fundus Perivasculitis Central retinal artery/vein occlusion Cystoid macular edema Vitreitis Exudative retinal detachment

- Anterior optic neuritis usually occurs in the late secondary stage of syphilis. It may develop during the course of syphilitic meningitis, or it may occur as an isolated phenomenon. Visual loss is rapid and usually associated with the development of visual field defects (Fig. 64.3).<sup>16</sup>
- Neuroretinitis is a condition in which anterior optic neuritis is associated with the deposition of lipids (hard exudates) in the papillomacular region (Fig. 64.4).<sup>17,18</sup>



**Fig. 64.3:** Optic neuritis with retinal hemorrhages in syphilis.



**Fig. 64.4:** Neuroretinitis with optic disc pallor.

- Retrobulbar optic neuritis may occur in patients with syphilitic retinitis, syphilitic meningitis, or syphilitic periosteitis that affects the orbit.<sup>19</sup>
- Papilledema may develop in patients with secondary syphilis as a result of increased intracranial pressure due to meningitis.<sup>20,21</sup>
- Optic atrophy appears as a sharply defined, pale optic disc with narrowing of retinal arterioles. About 5% of the patients with neurosyphilis develop optic atrophy.<sup>3,22</sup> Sometimes the presence of optic atrophy may be the sole manifestation. Involvement of the other eye usually occurs after months to years. Optic atrophy probably occurs as a result of endarteritis of the intramural small vessels with lymphocytic infiltration of pial sheath of the optic nerve.<sup>11</sup>

## Cranial Nerves

Cranial nerve palsies are most often caused by syphilitic basilar meningitis.<sup>2</sup> Other causes include gummas along the nerves, brainstem infarcts, and periosteitis of the superior orbital fissure. Syphilitic vascular changes can produce aneurysms and even subdural hematomas with cranial nerve manifestations. Trigeminal neuralgia with severe pain can occur secondary to syphilitic meningitis or osteitis of the periosteal bone. Lagophthalmos can occur from nuclear or supranuclear degeneration. Cases of vestibular nystagmus and periodic alternating nystagmus have been reported.<sup>23</sup>

## Visual Field Defects

Various types of visual field defects can occur in ocular syphilis depending upon the involvement of the visual pathway (Table 64.3).<sup>24</sup>

### Pupil

The classical pupillary finding in syphilis, the Argyll Robertson pupil, is usually seen in tertiary syphilis. The pupils are unequal, irregular, and profoundly miotic. Pupillary constriction in response to light is weak or absent but is normal or exaggerated in response to accommodation. The basal miosis is unaffected by exposure to dark and painful stimuli. The dissociated response is due to interruption of intranuclear neurons connecting the Edinger–Westphal nucleus with other pretectal nuclei.

Other causes of Argyll Robertson pupil include diabetes mellitus, alcoholism, encephalitis, and multiple sclerosis.<sup>25</sup>

### Interstitial Keratitis (IK)

This is the most common corneal manifestation of congenital or acquired syphilis.<sup>22,26,27</sup> Although spirochetes can invade the fetal cornea, interstitial keratitis is immune mediated. Maternal therapy before the second trimester, or treatment of the infant before the age of 3 months, can prevent interstitial keratitis.<sup>7,26–28</sup>

**Interstitial Keratitis in Congenital Syphilis** This is usually a late finding. Most cases manifest between the ages of 5 and 20 years. Acute IK may be triggered by ocular surface inflammation or following intraocular surgery. It most often affects the deep stromal layers either as multifocal infiltrates or as a diffuse process. Corneal stromal edema may result from the inflammation, resulting in a ground glass cornea. Variable degrees of deep corneal stromal neovascularization may be present, depending on the severity of the inflammation. Typically, the neovascularization begins at the corneal limbus. Stromal inflammation overlying the vessels often causes a salmon colored patch due to the pinkish color imparted by the stromal vessels. Intrastromal hemorrhage may also occur.

Interstitial keratitis may finally result in scarring of the corneal stroma and collagen remodeling. The superficial vessels are reabsorbed and the deeper vessels may be constricted resulting in ghost vessels that are seen as a late finding of syphilitic IK.

**Table 64.3:** Visual Field Defects in Ocular Syphilis

Type of lesion	Type of visual field defect
Syphilitic choroiditis	Ring scotoma
Optic neuritis	Central scotoma
Tabetic optic atrophy	Peripheral constriction with central or cecocentral scotoma or sectoral defect
Syphilitic basilar meningitis	Irregular bitemporal or rarely, binasal hemianopia
Syphilitic arteritis affecting middle cerebral artery	Complete or partial homonymous hemianopia or quadrantanopia

Congenital syphilitic IK is typically bilateral in 80% of cases.<sup>28</sup> Very rarely, both eyes are involved simultaneously. Usually, following inflammation of the first eye, the contralateral eye is affected may be after an interval of as short as 2 months or longer than 15 years.

**Interstitial Keratitis in Acquired Syphilis** Corneal disease in acquired syphilis is rare. Although interstitial keratitis may be seen, it is usually unilateral and may occur relatively early following primary syphilis. The patient presents with pain, photophobia, tearing, and blurred vision, similar to the symptoms seen in acute IK. In general, the symptoms are less severe and of a shorter duration.

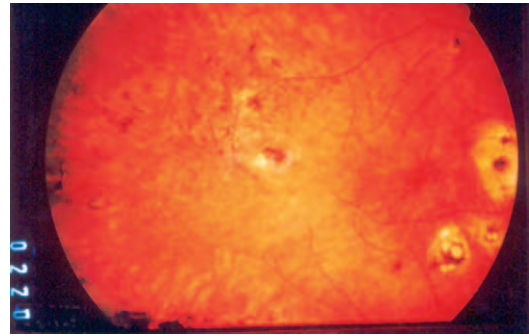
The clinical findings of IK in acquired syphilis very closely resemble those seen in IK in congenital syphilis. Late findings include an opacification of the stroma with ghost vessels and thinning. Endothelial changes in the form of redundant basement membrane at the level of Descemet membrane may also be present. Endothelial decompensation may follow, resulting in central corneal edema later in life.<sup>7,25,26</sup>

### Syphilitic Uveitis

Patients with syphilis can present with anterior uveitis, posterior uveitis, or panuveitis.

**Anterior Uveitis** Iridocyclitis in acquired syphilis is typically associated with a skin rash, but sometimes occurs as the only clinical sign in relapsing syphilis. It begins as an acute unilateral iridocyclitis that may be subclinical. The contralateral eye is affected in about 50% of the patients.<sup>7,14</sup> Transient iris roseola, reddish spots, or engorged vascular tufts resembling mucocutaneous lesions may precede the uveitis. Syphilitic uveitis commonly presents as a granulomatous inflammation. It may manifest as iris nodules which are similar in appearance to those seen in other granulomatous diseases. Vascularized nodules or papules at the pupillary border and near the root of the iris may occur during secondary or gummatous tertiary syphilis and lead to sectoral iris atrophy.<sup>28</sup> Iris and ciliary body gummata may also occur.<sup>13</sup> Ciliary body gumma may protrude into the anterior chamber angle as a brownish mass and even penetrate the scleral wall. The severity of the anterior uveitis can vary from a mild iritis to chronic iridocyclitis with hypopyon, anterior vitreous cells and cystoid macular edema.<sup>14,29</sup>

**Posterior Uveitis** A sprinkling of pigmented and depigmented spots (salt and pepper fundus) is a common feature of congenital syphilis. The posterior segment in acquired syphilis can manifest in different forms, such as vasculitis, macular edema, stellate maculopathy, pseudoretinitis pigmentosa, and neuroretinitis.<sup>3,7,14</sup> Other presentations include diffuse chorioretinitis (Fig. 64.5), uveal effusion, central retinal vein occlusion (CRVO), subretinal neovascular membrane formation, and exudative detachment.<sup>14</sup> Necrotizing retinitis can occur and may lead to neovascularization with vitreous hemorrhage or tractional bands between the disc and macula. Gumma of the choroid and retina may also occur. In HIV-infected individuals, large, yellowish placoid lesions



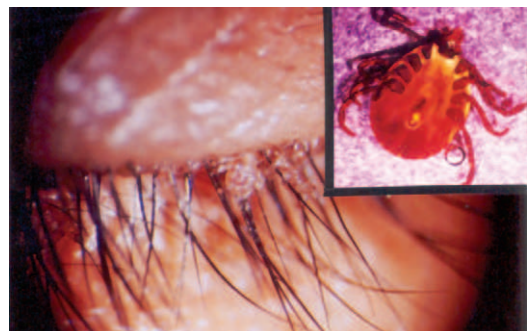
**Fig. 64.5:** Diffuse chorioretinitis in a patient of secondary syphilis.

are seen with atrophic centers with or without hemorrhage in macular or juxtapapillary region which are located at the level of retinal pigment epithelium. Gass, in 1990, coined the term “syphilitic posterior placoid chorioretinitis” when he described 6 patients with secondary syphilis who showed similar types of lesion.<sup>30</sup> The fluorescein angiogram characteristically shows early hypofluorescence and late staining of the lesions, and are often termed as “leopard spot” hypofluorescence.

### DIAGNOSIS OF SYPHILIS

A diagnosis of ocular syphilis is based on a clinical suspicion which can be confirmed by appropriate diagnostic tests. Dark field microscopy involves direct identification of *Treponema pallidum* by examining exudates from a chancre or condyloma latum. In syphilitic infection, there is production of nonspecific antibodies which react to cardiolipin. This forms the basis of traditional nontreponemal tests such as Venereal Disease Research Laboratory (VDRL) tests and rapid plasma reagin tests. On the other hand, the treponemal tests like *Treponema pallidum* particle agglutination (TPPA) detect antibodies against *Treponema pallidum*. The serological tests used for the diagnosis of syphilis are summarized in Fig. 64.6.

The nontreponemal tests show a decline in titres or become nonreactive with treatment, so they can be used to assess the response to treatment. Treponemal tests generally remain reactive



**Fig. 64.6:** Crab louse on the eyelashes along the lid margin.



for life. These tests are associated with a lower incidence of false positivity and they are more specific.

For diagnosis of neurosyphilis, there is no definite test. Although VDRL-CSF is highly specific, it is insensitive. Although, the CSF TPPA is less specific for neurosyphilis than CSF VDRL (i.e., yields more false positive results), it is highly sensitive. As syphilitic uveitis or other ocular involvement is frequently associated with neurosyphilis, a CSF examination needs to be considered for confirmation of diagnosis.<sup>31</sup>

## SYPHILIS AND HIV INFECTION

Concurrent infection of syphilis with HIV has been suggested to be more aggressive than syphilis alone. Syphilis can be rapidly progressive and relapses frequent in HIV-infected patients.<sup>32-34</sup> Ophthalmic manifestations of syphilis may occur during or shortly after the secondary stage (Table 64.4).<sup>35</sup> Anterior uveitis is the most common presentation, but posterior uveitis (panuveitis) also occurs.<sup>36</sup> Ocular syphilis in an HIV-infected patient is often accompanied by neurological involvement. Neuro-ophthalmic syphilis may also be the presenting feature of HIV infection. As in HIV seronegative patients, syphilis can present in HIV-infected patients with a wide variety of ocular manifestations including retinitis, neuroretinitis, optic neuritis, perineuritis, papillitis, retinal detachment, vitritis, and optic nerve gumma. However, ocular complications of syphilis may be more severe and frequent and may develop earlier in HIV-infected individuals.<sup>35-38</sup> Because of syphilis, posterior segment and neuroophthalmic lesions are more common in HIV-infected individuals.

## CLINICAL PEARLS IN OCULAR LESIONS OF SYPHILIS

- Syphilis is a great mimicker. Always keep this condition in mind in patients with cranial neuropathies, optic neuropathies, anterior uveitis, chorioretinitis, retinal vascular occlusion, and chronic anterior segment inflammation.
- Manifestations of syphilis can be complicated by concurrent HIV infection. Always screen patients with syphilis for HIV infection. Further, concurrent infections with gonorrhea and Chlamydia may frequently occur and should be investigated accordingly.
- Nearly 45% of males manifesting bilateral tonic pupils will test positive for syphilis.
- Lyme disease, another spirochetal disease, can mimic syphilis. In fact, Lyme disease can cause false positive specific and

**Table 64.4:** Common Ocular Manifestations of Syphilis in HIV-infected Patients

Anterior segment	Posterior segment	Neuro-ophthalmic
Anterior uveitis	<ul style="list-style-type: none"> <li>• Diffuse vitritis</li> <li>• Posterior uveitis or Panuveitis</li> <li>• Exudative retinal detachment</li> <li>• Necrotising retinitis</li> </ul>	<ul style="list-style-type: none"> <li>• Neuroretinitis</li> <li>• Papillitis</li> <li>• Perineuritis</li> <li>• Retrobulbar neuritis</li> </ul>

nonspecific tests for syphilis. Always consider Lyme disease as a possibility when testing for syphilis, particularly in cases where a history of high-risk sexual behavior is absent. In these cases, particularly in endemic areas, try to elicit a history of tick bite.

- Stromal interstitial keratitis is primarily a manifestation of congenital syphilis, but may occur in acquired syphilis. Interstitial keratitis is treated with high doses of potent topical steroids as this is inflammatory in nature and not actual stromal infection.

## TREATMENT OF OCULAR SYPHILIS

Parenteral penicillin G is the drug of choice for the treatment of all stages of syphilis. Ocular syphilis is a form of neurosyphilis and requires the same therapy. The therapy for ocular syphilis with concurrent HIV infection is the same as that for neurosyphilis in seronegative patients.

## Neisseria Gonorrhoeae and Eye Lesions

Gonorrhea is a major sexually transmitted infection worldwide, although up to 80% of women and 10% of men are asymptomatic.<sup>1</sup> In the newborn, *Neisseria gonorrhoeae* may result in ophthalmia neonatorum (neonatal conjunctivitis). This presents as acute or hyperacute conjunctivitis within the first few days of life. If untreated, it may rapidly progress to corneal ulceration and perforation. Such infection in an immunologically immature child can lead to sepsis and death.<sup>45,46</sup>

The differential diagnosis of neonatal conjunctivitis is given in Table 64.5.

Ocular infection in adults usually results from autoinoculation of the conjunctiva by a person with genital gonorrhea.<sup>48</sup> Gonococcal conjunctivitis is usually severe, with an overtly purulent exudate and the evaluation of any patient with severe purulent conjunctivitis should include a detailed sexual history, genital examination, Gram stain, and culture. In adults, *N. gonorrhoeae* infection presents as a hyperacute, mucopurulent conjunctivitis or keratoconjunctivitis. It progresses rapidly with edema of the eyelid and conjunctiva. Corneal epitheliopathy often occurs due to the toxicity of the discharge. *N. gonorrhoeae* is one of the few organisms that can penetrate the intact corneal

**Table 64.5:** Differential Diagnosis of Neonatal Conjunctivitis

Disease	Onset	Laboratory tests	Treatment
Chemical conjunctivitis	24 hrs	None	Observation
Inclusion conjunctivitis	5–14 days	Mixed cellular reaction in smear	Erythromycin
Gonorrhea	3–5 days	Gram-negative diplococci in smear	Penicillin/ceftriaxone
Neonatal herpes	3–21 days	Positive fluorescent antibody test	Topical and systemic antivirals

epithelium. The patient experiences tenderness and aching of the globe, and palpation reveals a prominent preauricular node. Delays in diagnosis and treatment may result in corneal ulceration and scarring.

### DIAGNOSIS AND MANAGEMENT

The use of culture and sensitivity testing from the primary site of inoculation is essential. Preliminary Gram stains can direct the initial therapy. Gram stain has a high specificity (99%) and sensitivity (>95%) in the diagnosis of gonococcal conjunctivitis. It usually shows polymorphonuclear leucocytes with intracellular gram negative diplococci, but a negative gram stain does not rule out infection with *Neisseria gonorrhoeae*.<sup>31</sup> In the treatment of neonatal conjunctivitis, both topical and systemic therapies should be initiated. Topical aqueous penicillin 10,000 to 20,000 U/mL instilled every hour for first 6 to 12 hours followed by every 2–3 hours till resolution. An alternative treatment is topical tetracycline ointment every 2 hours. Treatment of hyperacute gonococcal infections in adults involves aggressive systemic antibiotic therapy. Ceftriaxone is the drug of choice in treating adult and neonatal gonococcal ophthalmia.<sup>31,42</sup> Spectinomycin is an alternative for patients allergic to ceftriaxone.<sup>43</sup>

### Chlamydia Trachomatis and Eye Lesions

Chlamydia infection is the most common sexually transmitted disease in the developed world.<sup>39,44,45</sup> The organism implicated is *Chlamydia trachomatis* and transmission occurs via direct exposure to infected genital secretions. In the past, poorly chlorinated swimming pools and hot tubs were implicated as well, although this route of infection has been questioned.<sup>39,45</sup>

Neonatal transmission may occur during vaginal delivery. Inclusion conjunctivitis in adults occurs in one out of 100–300 cases of genital chlamydial infection.<sup>46,47</sup> However, more than half of all individuals diagnosed with chlamydial eye disease manifest a concomitant genital infection.<sup>47</sup>

In adults, an acute or subacute follicular conjunctivitis typically ensues after an incubation period of about 5 days. A unilateral or asymmetric presentation is more common. Symptoms may include foreign body sensation, photophobia, redness, lid swelling, and sticky, mucopurulent discharge from the involved eye, which may cause difficulty in opening the eye lids upon awakening.

Slit lamp biomicroscopy reveals moderate injection of the bulbar conjunctiva with variable edema. One may also observe a prominent follicular reaction and, to a lesser extent, papillary hypertrophy. Corneal involvement may occur about 2 weeks after the onset of conjunctivitis in the form of a punctate epithelial keratopathy with or without subepithelial infiltrates. If untreated, vascularization and pannus may ensue. Anterior uveitis may also accompany inclusion conjunctivitis, most commonly in those with a history of collagen vascular disorders. On palpation a nontender preauricular lymphadenopathy on the side of the involved eye is almost always detected.

### DIAGNOSIS AND MANAGEMENT

The diagnosis of inclusion conjunctivitis is based on the clinical presentation, and a history of genital infection and related symptoms.<sup>47</sup> One should suspect chlamydial infection if a chronic follicular conjunctivitis resists topical therapy for some weeks. Various tests are available to diagnose ocular chlamydial infections including culture, direct fluorescent antibody test (DFA), and nucleic acid amplification test.

Systemic antibiotics are the treatment of choice for inclusion conjunctivitis. While topical therapy may ease the ocular symptoms, it will not affect the cure. Azithromycin 1 g orally in a single dose or doxycycline 100 mg orally twice a day for 7 days are the drugs of choice in adults. Erythromycin 50 mg/kg/day orally divided in to four doses daily for 14 days is recommended for Chlamydia ophthalmia in neonates.<sup>31</sup>

### Herpes Simplex Virus (HSV) and Eye Lesions

The virus occurs in two forms: HSV type 1, which has traditionally been implicated in ocular and oral herpes infections; and HSV type 2, which had been considered primarily a cause of genital herpes. Eighty per cent of the neonatal HSV infections are caused by HSV type 2. With changes in sexual behavior, the frequency of the HSV type 1 infections occurring in the genital area has risen since the 1970s.<sup>48</sup>

Human beings are the only natural host of the herpes simplex virus. Transmission typically occurs by direct contact with an open epithelial lesion or contaminated body secretions. Rarely, the virus may spread through contaminated materials such as towels or tissues. As with other STIs, herpes simplex can cause ophthalmia neonatorum due to transmission from an infected mother (neonatal HSV). The features of the neonatal HSV are described in Table 64.6.

In herpetic eye disease secondary to genital infection, the onset typically occurs 1–2 weeks after the eruption of the genital lesions. Symptoms of ocular HSV infection may include photophobia,

**Table 64.6:** Manifestations of Neonatal Ocular HSV

#### Manifestations of neonatal ocular HSV

- Periocular vesicles
- Conjunctivitis
- Keratitis
  - A. Epithelial
  - B. Stromal
- Inflammation
  - A. Anterior uveitis
  - B. Vitritis
- Lenticular opacities (i.e., cataract)
- Retina
  - Vasculitis
  - Retinitis
  - Retinal detachment
  - Chorioretinal scars
  - Exudate
- Optic neuritis

**Table 64.7:** Manifestation of Adult Primary Ocular Herpes Simplex

Constitutional	Ocular diseases
Malaise	Blepharitis
Fever	Conjunctivitis
Myalgias	Epithelial keratitis
Lymphadenopathy	Subepithelial infiltrate
	Interstitial keratitis
	Disciform keratitis
	Uveitis
	Retinitis

epiphora, foreign body sensation, and blurred vision. Clinical signs include follicular conjunctivitis, blepharitis and keratitis. Small vesicles arise on the lid margin and periocular skin, which then ulcerate and produce edema leading to an erosive dermatitis. Conjunctival follicles and punctate keratopathy, with or without subepithelial infiltrates, may follow (Table 64.7).

After the initial infection, the virus lies dormant within the trigeminal, ciliary and/or the superior cervical ganglia. Recurrences of ocular HSV almost invariably strike the cornea, and about 50% of patients get recurrent infections within the first 5 years.<sup>49</sup>

HSV keratitis typically presents as a unilateral red eye, with variable pain or irritation. Photophobia and epiphora are common. Vision may or may not be affected, depending on the location and extent of the corneal lesion. The hallmark of HSV keratitis is a dendritic epithelial lesion. Each recurrent attack augments damage to the corneal nerves, which eventually leads to hypoaesthesia. Following dendritic keratitis, disciform stromal keratitis may develop in some cases. This presents as a central dense area of inflammation and edema surrounded by immune cells, known as a “Wessely ring.” Late complications of recurrent HSV ocular infection may include necrotizing interstitial keratitis, chronic uveitis, and secondary glaucoma.<sup>50</sup>

One of the most visually devastating consequences of posterior segment involvement is acute retinal necrosis. It is a vaso-occlusive angiitis of chorioretinal vessels along with necrotizing retinitis. Acute retinal necrosis typically starts in the periphery and can lead to retinal detachment.

Table 64.7 summarizes the ocular lesions due to herpes simplex.

## DIAGNOSIS AND MANAGEMENT

Primary ocular herpes infection should be suspected in patients with unilateral blepharoconjunctivitis and vesicular lid lesions. Scrapings, blood tests, and detection from the vesicles may help confirm the etiology. Recurrent HSV infection can usually be diagnosed by clinical observation alone, although laboratory tests are required to confirm it. In cases with diagnostic dilemmas, real-time PCR with corneal epithelial scrapping, tear fluid has been found to be useful.

HSV infections are typically self-limiting and usually resolve within 10–14 days. Symptomatic vesicular lid lesions

can be managed with warm compresses. Topical steroids are contraindicated for HSV lid lesions, as they may predispose to corneal involvement.<sup>51</sup>

Recurrent HSV corneal epithelial infections require prompt and aggressive therapy to prevent corneal scarring. The treatment consists of the application of topical trifluridine 1%, up to nine times daily. As the dendritic ulcers regress, medicines are tapered until complete resolution, usually within 7–10 days. After that, the medication should be continued three times daily for another week to ensure complete suppression of the virus. Debridement of the ulcer bed is advocated by some, but there is no proof that this speeds up the resolution or improves the visual outcome. Cycloplegia is indicated for associated uveitis.

Disciform stromal keratitis presents a greater clinical challenge, as it can lead to permanent visual loss. Therapy aims to reduce the inflammation. Cycloplegia is again recommended.<sup>5</sup> In a herpetic eye disease study, it was observed that topical steroids reduced the persistence and progression of stromal inflammation, and shortened the duration of HSV stromal keratitis thereby establishing the benefit of topical corticosteroids in addition to topical antivirals in the treatment of HSV stromal keratitis.<sup>52</sup> Weaker steroids, such as 0.125% prednisolone acetate, or 1% prednisolone sodium phosphate, are preferred. It is advisable to taper the steroids slowly over 10–16 weeks. Concurrent therapy with topical trifluridine, four to five times a day, is essential. Oral acyclovir 400 mg twice a day for 1 year or more has been found useful in prevention of recurrent herpetic disease in patients who have demonstrated a tendency for recurrence.<sup>53</sup>

For the management of neonatal herpetic disease, emergency pediatric or infectious disease consultation should be obtained with reference to initiating immediate intravenous therapy with acyclovir, as there is a definite association between ocular neonatal HSV and potentially lethal systemic or neurological infection. The treatment of focal ocular disease is with topical antivirals in addition to systemic acyclovir regardless of whether the etiologic agent is HSV type 1 or 2. A full ocular antiviral regimen should be instituted immediately. Povidone-iodine gel or ophthalmic bacitracin can be used to minimize the risk of secondary infections.

Treatment of acute retinal necrosis includes prompt initiation of intravenous antiviral medication with acyclovir, in addition to oral steroids to reduce inflammation.<sup>54</sup>

## Crab Louse Infestation

The louse family includes two genera, *Pediculus humanus* and *Phthirus pubis*.<sup>55,56</sup> The most common eyelash infestation is from the pubic louse, and is known as *Phthiriasis pubis palpebrarum*. The pubic crab louse has a predilection for eyelashes and pubic hair because the spacing between the follicles is ideally suited for its grasping apparatus. The most common mode of infestation is hand contact with the genital area. It can also follow orogenital contact. Crab louse infestation presents with pruritic lid margins and blepharoconjunctivitis (Fig. 64.6). Occasionally, preauricular



lymphadenopathy may occur if bites result in a secondary infection. Patients often come with complaints of lid irritation and itching, and it is often misdiagnosed as conjunctivitis. A detailed slit lamp evaluation will reveal crusty, blood-tinged deposits along the lid margins. One may also detect reddish brown fecal matter at the base of the eyelashes.

Diagnosis is confirmed when one observes a louse. One can also usually see white nits, unhatched eggs in the form of oval deposits in the lashes. Reinfestation occurs as the nits hatch following treatment of the adult mites.<sup>57</sup>

## MANAGEMENT

Physical removal of the lice and nits is important, but usually does not totally eradicate the infestation. Supplemental therapy is necessary. Smearing bland petroleum jelly into the lashes in an effort to smother the adult lice or the use of bacitracin ointment, which may also help eradicate a concurrent staphylococcal infection, is useful. Since the nits are immune to this therapy, patients should use the ointment for at least 2 weeks to smother new hatchlings. In addition, use of physostigmine 0.25% (Eserine) ointment will poison the respiratory system of the adult mites. This treatment likewise must extend at least 2 weeks to cover the life cycle of the louse and eradicate the hatchlings.

Alternative ointments for this purpose include yellow mercuric oxide N.F. 1% or ammoniated mercury 3%. Sodium fluorescein used in fluorescein angiography can also be effective. One should keep in mind that the primary infestation involves the genitalia and successful treatment mandates removal of all organisms. Available pediculocides include lotions and shampoos containing g-benzene hexachloride and pyrethrin. A single application is generally sufficient, but reapplication 1 week later will ensure eradication. Because of their toxicity, these pediculocides cannot be used to treat eyelid infestation. Also, given their neurotoxicity, these medications should be used with extreme caution in children and pregnant women.<sup>55-57</sup>

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# Arthritis Associated with Sexually Transmitted Infections

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65

## Introduction

Patients suffering from sexually transmitted infections (STIs) may have acute or chronic joint involvement.<sup>1</sup> Although this may not be a frequent occurrence, severe articular disease can be both incapacitating and deforming. There is a wide clinical spectrum of articular involvement and usually only the severe forms are seen at referral centers. Many more patients have mild joint pain, which is often ignored. Further, some forms of joint involvement may be self-limiting and are thus of less clinical importance.

However, some distinct articular syndromes are associated with STIs, and these are observed fairly regularly and are well-established clinical entities.<sup>1,2</sup> Direct invasion of the joints results in the syndrome of septic arthritis and immune mechanisms triggered by the STI result in an immunologically mediated Sexually Acquired Reactive Arthritis (SARA). Detailed studies of this phenomenon have clearly established a close link between infection and arthritis. As this form of arthritis usually presents acutely, soon after the triggering infection, the interaction between the organism and the host mechanisms is easier to study and establish in this group of conditions than in a disease like rheumatoid arthritis, which is, most often, far more insidious in onset. Several elegant experimental and clinical studies have pieced together a better understanding of the interplay between the host and the pathogen.<sup>3,4</sup> Several animal models, closely mimicking human disease, have also been developed to facilitate research.<sup>3,4</sup>

Among the STIs, gonorrhea, syphilis, chlamydial infections, lymphogranuloma venereum, infection with Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), Hepatitis C virus (HCV), mycoplasma, genital herpes and cytomegalovirus (CMV) have all been implicated in the development of arthritis. Several of these associations have a rich and colorful history.

## History

The relationship between sexual activity and joint diseases was initially recognized by Hippocrates. He proposed that young men

do not get the gout until they are sexually active. At that time all forms of articular disease were referred to as gout. For the next 600 odd years no further developments were recorded. In 300 AD, the development of arthritis following dysentery was noted. As there is close similarity between the development of arthritis following STIs and gastrointestinal tract infections, they will be considered together for the purpose of this historical review.<sup>5-7</sup>

Van Foreest, in 1575, documented the association between urethritis and knee arthritis, and in 1664 Martinere recorded an epidemic of this phenomenon during a military campaign. Seydenham, Morton, and Willis noted this association with arthritis in the great dysentery epidemics between 1668 and 1672. It was, however, Musgrave who noted for the first time in 1715 an association between a venereal disease and arthritis. This relationship was not easily accepted by the medical establishment and John Hunter, in his "Treatise on the Venereal Disease" (2nd ed., 1788), noted that he had never seen "venera attack the joints".<sup>7</sup>

Over the next few years better documentation of observations led to a change in stance. Swediaur, initially in French and later in English, gave a masterly description of knee joint, and later calcaneal swelling after blennorrhagicum. By 1810, the third edition of Hunter's Treatise had changed sufficiently to dub venereal diseases "the seat of rheumatism".<sup>7</sup>

There have been several historical descriptions of arthritis in patients with syphilis and gonorrhea. Gonococcal arthritis was probably first described by Seydenham in 1734 but became an established clinical entity in the later half of the 19th century when Neisser isolated and identified the organism. The relationship of arthritis with syphilis was often mentioned in the older literature. However, with effective treatment and better delineation of other articular syndromes this association is now infrequently reported.

In 1818, Sir Benjamin Brodie described six patients with a symptom complex comprising of urethritis, conjunctivitis, and arthritis. This report predated that of Hans Reiter by almost a century.<sup>6</sup> By 1836, 13 such patients had been recorded and they were recognized to be suffering from a distinct disease entity different from gonococcal arthritis.



In 19th century, two teaching institutions in London recorded that during two different periods of observation arthritis related to STIs comprised roughly 3% of all admissions for rheumatic complaints.

The impact of this form of arthritis related to either GI tract infection or STIs was felt by the military establishment. Troops and sailors were the frequent victims of epidemics of these infections and the British fleet in the Caribbean was virtually incapacitated by dysentery-related articular syndromes in 1804. In the Crimean war, 1200 (13%) of the 9500 soldiers invalided out of service were suffering from arthritis. Several historical figures are also believed to have suffered from this form of arthritis including Christopher Columbus the explorer, and Cellini the master goldsmith and sculptor. Columbus suffered incapacitating arthritis and ocular inflammation during his historical voyages to the New World.<sup>8</sup>

In 1916, Reiter described a symptom complex, akin to that recorded earlier by Brodie, in a German officer who had suffered dysentery in the trenches during the World War I. The use of the term Reiter syndrome to describe a clinical entity characterized by urethritis, arthritis, and ocular inflammation initially gained momentum until Reiter's unsavory role in the next great war as a camp physician involved with human experimentation came to light.<sup>9</sup> In the 1960s, the term reactive arthritis was proposed and this has now become the accepted terminology.<sup>10</sup>

The HIV epidemic has profoundly affected the practice of rheumatology in southern Africa and other parts of the world where HIV is highly prevalent. HIV-related arthritis is less frequently observed in Caucasian and Indian populations when compared to Africans.

## Direct Joint Involvement

### GONOCOCCAL INFECTION

Direct joint involvement takes the form of septic arthritis in the context of sexually transmitted infections. The causative organisms are either *Neisseria gonorrhea* or rarely, *Ureaplasma urealyticum*. This arthritis is not related to HLA B27. It can be polyarticular and a part of the classic arthritis, dermatitis syndrome associated with disseminated gonococcal infection (DGI). There is usually no chronic joint inflammation, spondyloarthritis, or the development of the classic forms of reactive arthritis.<sup>1,11</sup>

Patients usually present with fever, joint pain, dermatitis, and synovial sheath inflammation for a few days. Fever is usually high grade but may occasionally be absent. The joint pains may be migratory with resolution of pain, swelling, and redness from the initially involved joint when the next gets affected, or additive where several joints are involved in succession with no resolution of symptoms in the initially involved joints. Synovial sheath swelling of the dorsal aspect of the hands and wrist may be the initial manifestation, while the first joints to be involved may be the knees or ankles. Joint pain may resolve spontaneously in about 30% of patients but evolve into classic septic arthritis of one or

more joints in the remainder. Hand joints, wrists, knees, ankles and feet are commonly involved. In the usual forms of septic arthritis, only one large joint is involved and hand joint involvement is very uncommon. However, the septic arthritis of DGI characteristically involves more than one joint and the small joints of the hand are frequently affected. The sternoclavicular joint, temporomandibular joint and sacroiliac joints are seldom involved. In a minority of patients a symmetric polyarthritis may be noted.<sup>12</sup> Additional factors that contribute to the development of septic arthritis include concomitant HIV infection, malignancy, chemotherapy, diabetes, systemic lupus erythematosus, complement deficiencies, and intravenous substance use. The joints are swollen, red, and tender with synovial thickening and effusion along with limitation of movement. Joint radiology is usually non contributory due to the acute nature of the infection. Synovial fluid shows a brisk leukocytosis and culture is often positive. The blood culture is positive in a smaller percentage.<sup>11,13</sup>

When gonococcal septic arthropathy is suspected, samples should be sought from the cervix, urethra, pharynx, and rectum. In DGI, 50% of patients have a positive result for one of these mucosal sites. Gonococci are fastidious organisms to grow and require specific conditions. Nucleic acid testing from samples of synovial fluid can also help confirm the nature of the infection.

The skin lesions (Fig. 65.1) associated with this syndrome are described in detail in the chapter on DGI. In summary, they comprise tiny pustules or vesicles with a reddish base. These are neither itchy nor painful and are most often found on the extremities.

Patients may rarely show other features of DGI, namely, endocarditis, myocarditis, perihepatitis, pelvic inflammatory disease, and overwhelming sepsis with adrenal insufficiency and adult respiratory distress syndrome.<sup>11,13</sup>

Chronic arthritis due to gonococcal infection is extremely uncommon unless there has been inadequate treatment or the organism is resistant to the prescribed antibiotics. Serious joint destruction can be the consequence of such a problem. Occasionally, a gonococcal osteomyelitis may supervene due to direct extension from an infected joint.

There is a large differential diagnosis for the syndrome of fever, skin lesions, joint pains, and tenosynovitis. *Listeria*, *Staph. aureus*, coxsackie virus, echovirus, Epstein-Barr virus, cytomegalovirus, Hepatitis B, Hepatitis C, parvovirus B19, falciparum malaria, *Vibrio* infections and vasculitides can present in similar fashion. However, in the setting of STIs, it is important to differentiate the septic arthritis of DGI from a reactive arthritis. This condition tends to have a slower evolution over weeks rather than days and usually affects the lower limb in preference to the upper limb. Conjunctival inflammation and painless mucosal ulceration are important features, which are usually missing in patients with DGI. Further, the urethritis in reactive arthritis tends to be milder and less painful than that observed in gonorrhea.<sup>1,11,13</sup>

The management of patients with DGI and arthritis is with parenteral antibiotics based on antimicrobial sensitivity

testing. Response to adequate antibiotic therapy is usually prompt and the outcome excellent. Patients should be educated regarding the use of condoms and the treatment of sexual partners.

## Indirect Joint Involvement

### SYPHILIS

The re-emergence of syphilis as an important STI, especially in relation to HIV infection, is a major public health problem. This clinical setting provides ideal ground for atypical manifestations, an aggressive clinical course, an altered serologic response and sometimes a poor therapeutic response. Several long forgotten manifestations of syphilis need to be reviewed and osteoarticular complications are just one of them.<sup>1,14</sup>

Articular manifestations of syphilis were well-recognized in the preantibiotic era and comprise several clinical forms. Osteochondritis, osteitis, periostitis, and gumma of bone are well-recognized manifestations of congenital syphilis, while polyarthralgia, polyarthritis, spondylitis, tenosynovitis, and neuropathic arthropathy are features of secondary and tertiary syphilis.<sup>14</sup>

Osteochondritis affects the ends of long bones and manifests within the first six weeks of life. It responds well to treatment with penicillin. Osteitis and periostitis involve the shaft of long bones and show a similar response to therapy.

Between 5% and 10% of patients with secondary syphilis have joint pain.<sup>15</sup> An inflammatory arthritis, characterized by swelling and tenderness, is less frequent. When it occurs, it is symmetrical and mainly involves the large joints. It can thus be a differential diagnosis of rheumatoid arthritis. Although electron microscopy of synovial tissue from such patients has shown bodies that look like treponemes,<sup>16</sup> demonstration of the organisms by conventional methods has not been successful. Some patients with pain in the back mimicking spondylitis have also been described. These forms of articular disease respond well to treatment for syphilis.

In tertiary syphilis, joint involvement is usually due to neuropathy associated with tabes dorsalis.<sup>14</sup> Rarely, gumma of bone or joint may be found. The neuropathic joint is painless, is grossly swollen, and shows no features of inflammation. Radiologically, the bones show gross destruction and severe disorganization of the joint structure. There is invariably a large soft tissue swelling. The ends of the bones, surprisingly, do not show osteoporosis. A neuropathic joint requires support, splinting, and orthopedic fixation to optimize function.

### LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum may be associated with the development of a rash, symmetrical polyarthritis, and a positive rheumatoid factor.<sup>1</sup> It could thus be a differential diagnosis of rheumatoid arthritis. This is an infrequently observed syndrome and its exact pathogenesis is unknown. Treatment of the underlying infection is usually followed by a good response.

### HEPATITIS B VIRUS INFECTION

Although arthritis in patients with jaundice was recorded over 150 years ago, its importance was recognized in 1970s. Arthralgia is a frequent component of the prodrome of hepatitis B affecting almost 50% of patients. About a third of these patients may actually develop a symmetrical arthritis of the hands, feet, knees, and ankles. An urticarial rash is observed in half the patients who develop the arthritis. The arthritis is usually self-limiting and tends to disappear with the appearance of jaundice.<sup>1</sup> Occasionally, patients with hepatitis B infection go on to develop polyarteritis nodosa. This form of systemic necrotizing vasculitis has protean clinical manifestations dominated by fever, weight loss, joint pain, mononeuritis multiplex, hypertension, testicular infarction, bowel ischemia, and renal infarction.<sup>17</sup> Patients may be deceptively normal looking with a potentially catastrophic illness lurking underneath. A high degree of suspicion is required. Some patients may demonstrate antineutrophil cytoplasmic antibodies (ANCA).<sup>17</sup> Immune suppression, plasmapheresis, and interferon therapy have all helped to reduce the previously high mortality.<sup>17</sup>

### Reactive Arthritis

Reactive arthritis is defined as sterile joint inflammation following distant infection.<sup>10,18</sup> It may be triggered by genitourinary infection, gastrointestinal infection, or an upper respiratory infection. It is a systemic disease of worldwide distribution with an equal sex ratio if acquired after a gastrointestinal or respiratory infection. The ratio of males to females in those who have sexually acquired reactive arthritis is close to 9:1. In general, reactive arthritis involves mainly young adults with a prevalence of 30–40/100,000 and an incidence of 5–28/100,000 per year reported in Finland. It has a strong association with HLA B27, which results in a near 50-fold increase in the probability of SARA. It follows a variable, usually self-limited course and predominantly affects the joints, skin, mucous membranes, eye, heart and blood vessels, and occasionally other organs or systems like the kidneys.<sup>1,18,19</sup> Approximately 15% of patients will, however, develop chronic joint problems.

Patients with reactive arthritides show involvement of the axial and peripheral joints as part of a spectrum where enthesitis is an important pathologic hallmark.<sup>20</sup> This is the area where tendons and ligaments attach to bones. Classification and diagnostic criteria have been established.<sup>21–23</sup> The study of these conditions in the clinic and the laboratory has afforded a unique opportunity to assess the range and impact of the interaction between the host and a group of microbes, away from the drama of an acute infection.<sup>24–30</sup>

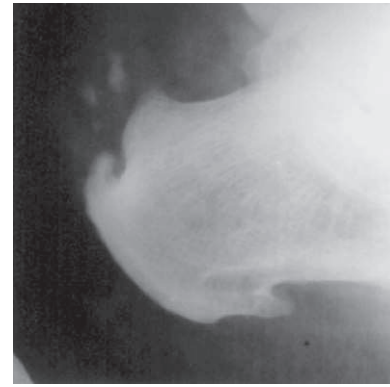
Articular involvement ranges from mild arthralgia to severely disabling polyarthritis. It is usually asymmetrical and can be in the form of a monoarthritis, oligoarthritis (less than four joints) or polyarthritis. Weight bearing joints of the lower limbs are most frequently involved.<sup>1,10,18</sup> Isolated involvement of an upper limb joint is very uncommon unless the patient also has psoriasis. The distribution is knee (80%); ankle and metatarsophalangeal (60%); tarsal, wrist, proximal interphalangeal of lower limbs

(40%); elbow, metacarpophalangeal and proximal interphalangeal of upper limb (30%); shoulder, distal interphalangeal (20%); hip, acromioclavicular, sacroiliac (10%); and sternoclavicular (5%). The arthritis may be migratory but is most frequently additive.<sup>18</sup> Since the disease affects mainly young people, the initial manifestations of reactive arthritis are often considered to be some form of sporting injury.<sup>3,18</sup> The entire pattern of involvement generally evolves over one to several weeks. Once it has developed, it may either resolve spontaneously or persist requiring medication. The duration of a single nonresolving episode of reactive arthritis may vary from 3 to 12 months. In the presence of concomitant HIV infection, the course of reactive arthritis is more aggressive. The HIV epidemic has seriously impacted the practice of rheumatology in sub-Saharan Africa. In Zambia, over a 30-month period, 98% of 128 undifferentiated spondyloarthritis patients and 87% of 130 with reactive arthritis were found to be HIV positive. These patients had longer episodes of arthritis and took longer to attain remission.<sup>31</sup>

Inflammation of the finger and toe joints along with subcutaneous tissue results in the development of a sausage shaped digit, which is tender and inflamed.<sup>1,18</sup> This dactylitis affects about 15% of patients and is an important clinical feature of reactive arthritis. It is usually asymmetric. These patients also tend to have asymmetric involvement of several joints including the sacroiliac joints.<sup>18</sup> The hallmark of this form of inflammation is enthesitis. In all forms of reactive arthritis the entheses are inflamed and produce a typical clinical and radiological picture.<sup>20</sup> The most frequent form of enthesitis in clinical practice involves the heel and plantar fascia (Fig. 65.1). However, other important areas that could dominate the clinical picture include the ischial tuberosity, iliac crest, ribs, and the tibial tuberosity.



**Fig. 65.1:** Lesions of disseminated gonococcal infection on palms and feet. Courtesy: Radha Rani Mittal, Patiala, India.



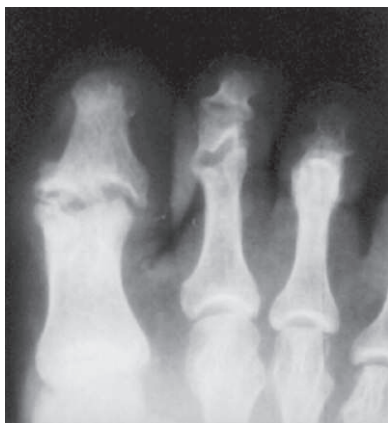
**Fig. 65.2:** Lateral radiograph of the ankle showing a well-developed calcaneal spur in both the tendo achilles and the attachment of the plantar fascia.

Radiologically there are a wide spectrum of abnormalities observed.<sup>18</sup> Enthesitis can result in either an erosion or a spur formation. These erosions differ from the erosions of rheumatoid arthritis because they are extra synovial and often in relation with the shaft of the bone (Fig. 65.2). The erosions in rheumatoid arthritis are synovial in distribution and marginal in location on radiographs. The other feature distinct from rheumatoid arthritis is new bone formation. This takes the form of either whiskering or spur formation (Fig. 65.3). Spur formation around the calcaneum is very typical of all forms of reactive arthritis. Similarly, spur formation can be observed in radiographs of the knees and other involved joints. Enthesitis and inflammation of the sacroiliac joints can result in initial widening followed by sclerosis, new bone formation, and ankylosis<sup>18</sup> (Fig. 65.4). However, this involvement is usually asymmetric unlike that observed in patients with ankylosing spondylitis. Spinal enthesitis in reactive arthritis results in the formation of large asymmetric syndesmophytes unlike the fine symmetrical syndesmophytes observed in patients with ankylosing spondylitis<sup>18</sup> (Fig. 65.5).

Skin involvement takes the form of keratoderma blennorrhagicum (Fig. 65.6 & 65.7). It starts as a reddish macule that thickens and enlarges to form papules and plaques. It is associated with hyperkeratosis and may be histologically indistinguishable from psoriasis. Most frequently, it involves the soles of feet followed by the palm of the hands and is painless. It is more frequently observed in patients with sexually acquired reactive arthritis than in those with a preceding enteric or respiratory infection.<sup>1,18</sup>

Nearly a third of patients with sexually acquired reactive arthritis develop painless ulcers over the buccal mucosa, lips, tongue, palate, tonsillar pillars or throat. A similar percentage develop painless genital ulcers. In men, they take the form of circinate balanitis (Fig. 65.6), which is a painless geographic dermatitis of the glans penis in uncircumcised men. These lesions tend to resemble keratoderma blennorrhagicum in circumcised men.<sup>1,18</sup> In women, an erosive vulval inflammation is sometimes observed. Urethritis is a common manifestation and develops in up to 90% of patients





\*c+



\*d+

**Fig. 65.3:** Hand radiograph showing (a) large extensive erosion involving even the shaft of the middle phalanx in a patient with reactive arthritis in distinction from (b) the marginal erosion of rheumatoid arthritis.



**Fig. 65.4:** Hand radiograph showing the development of a spur resulting in whiskering of the lower end of the middle phalanx.



**Fig. 65.5:** Radiograph showing asymmetrical sacroiliitis in a patient with reactive arthritis.



**Fig. 65.6:** Characteristic heaped up scale of reactive arthritis syndrome (Reiter's) with onycholysis.



**Fig. 65.7:** Palmoplantar lesions of reactive arthritis. Note the dystrophic nails.

during the course of their illness even if they are sexually inactive. In the sexually active, the usual tendency is to ascribe all urethral symptoms to an STI. However, the failure to demonstrate an organism and the lack of response to conventional antibiotics should alert one to the possibility of a reactive inflammation.<sup>18</sup> The development of other features of the syndrome confirms it. Involvement of the prostate, prostatic urethra, uterine cervix, and fallopian tubes has been documented

About 15% of patients with reactive arthritis develop subungual hyperkeratosis resulting in the thickening and lifting up of the nail from their beds and imparting a yellowish brown discoloration.<sup>1</sup>

Ocular inflammation can develop in nearly half the patients with sexually acquired reactive arthritis. It can manifest as a mild conjunctivitis that may be easily missed. The most serious involvement is in the form of uveitis, which may be recurrent. It is usually confined to the anterior segment of the eye and manifests

as blurred vision and circumcorneal congestion. Keratic precipitates and cells in the anterior chamber are the usual findings. Repeated episodes of uveitis may result in the formation of a complicated cataract, development of glaucoma or posterior uveitis. All these complications may seriously impair vision and ocular inflammation requires urgent treatment. This may include topical steroid drops along with mydriatics for the milder episodes, and either local subtenon injection of steroids or oral steroids for more severe inflammation.<sup>32</sup> The other rarer forms of ocular involvement include episcleritis, keratitis, and corneal ulceration.

Visceral involvement in reactive arthritis affects the cardiovascular system and occasionally the kidneys. Cardiovascular involvement manifests as abnormalities of atrioventricular conduction (5–10%), complete heart block, acute aortitis resulting in aortic incompetence, myocarditis, pericarditis, and heart failure. All these manifestations are potentially life-threatening and require urgent management.<sup>33,34</sup> This may include pacemaker implantation and high-dose corticosteroid therapy. Renal involvement is in the form of an IgA nephropathy. There are several other very infrequent systemic manifestations that may occur in such patients including pleuro pericarditis, pneumonitis, meningoencephalitis, peripheral neuropathy, and thrombophlebitis.<sup>1</sup> It is a clinical challenge to ascribe these manifestations to reactive arthritis at the outset and all such patients require detailed investigation to exclude commoner causes before such a conclusion can be reached.

Investigations do not usually provide a conclusive diagnosis regarding the cause of reactive arthritis.<sup>18,34</sup> There may be a leukocytosis and other evidence of inflammation, but tests for Rheumatoid factor and ANA are negative. The synovial fluid also shows leukocytosis. Elegant microbiological studies involving PCR have demonstrated fragments of chlamydial DNA in the synovial fluid of some patients supporting an etiological role for this organism in the genesis of reactive arthritis.

The clinical course of reactive arthritis is very variable. As stated previously, each episode may last from 3 to 12 months and occasionally even longer.<sup>34</sup> There is roughly a 10–15% risk of recurrence annually.

Joint inflammation can be controlled with a judicious use of the nonsteroidal anti-inflammatory drugs (NSAIDs). For persons with a history of gastrointestinal ulceration, it is wiser to use a selective COX-2 inhibitor like Celecoxib (200–400 mg/day). However, the pain is occasionally so severe that patients require large doses of indomethacin (100–200 mg/day), naproxen (750–1500 mg/day), piroxicam (20–40 mg/day), or diclofenac (100–200 mg/day) for control of inflammation. Oral and injectable corticosteroids are very helpful in the control of severe initial inflammation and also to control flares. Attempts should be made to try and taper the dose to the minimum, which is effective as soon as control over symptoms is achieved.<sup>18,34</sup> For patients with a predominantly peripheral arthritis, sulfasalazine therapy provides good control. This drug is also useful in the management of some patients with spinal pain. Treatment is usually started with 1000 mg/day and built up to 2–3 g. Blood counts need to be monitored regularly, and glucose 6 phosphate

dehydrogenase deficient patients and those with a known allergy to sulfonamides should not be given sulfasalazine. Methotrexate therapy is also useful in the management of peripheral reactive arthritis. It is desirable to exclude hepatitis B and C virus infection and establish normal liver function before starting therapy at 7.5–15 mg/wk. The dose can be gradually built up to 20–25 mg/wk if necessary with monitoring of liver function, renal function and the hematology profile.<sup>34</sup>

The role of antibiotics in the management of patients with reactive arthritis is controversial. Some small studies have shown a benefit but several others have failed to demonstrate any advantage. Macrolides, ciprofloxacin, doxycycline, and minocycline have been used but there is no convincing evidence of their efficacy in either preventing the development of reactive arthritis or in curtailing the course of the arthritis when it develops.<sup>3,34</sup>

The use of infliximab and etanercept in the management of such patients has been recommended recently.<sup>34,35</sup> Usually these patients have become refractory to other modalities of treatment and have active disease. While there is usually an excellent short-term clinical response, the long-term outcome of this treatment is not known. There have been several instances of patients on this therapy developing clinically significant tuberculosis, autoimmune disease, and allergic reactions. With the availability of a completely humanized molecule, and with a better understanding of the implications of such therapy in patients with infectious diseases including concomitant HIV infection, the true place of biological therapy will emerge.<sup>34</sup>

## PATHOGENESIS

The role of infection in the development of arthritis has been speculative. In the case of rheumatoid arthritis, the lack of a temporal correlation has raised serious doubts regarding the validity of such a presumption. In the case of reactive arthritis, the close time-event relationship has made establishing this relationship a little easier. Elegant studies on patients, their genetic constitution, their serologic responses, synovial fluid characteristics and developments in the field of microbial identification and microbial gene expression have all resulted in the elucidation of a clearer road map to follow in the development of this condition.<sup>3,4,35,36</sup> Animal models have also contributed



**Fig. 65.8:** Dermal manifestations of reactive arthritis. Circinate balanitis.

significantly to the development of a clearer picture. The following section is based on the understanding reached in relation to chlamydial infection and its interaction with the host to produce articular inflammation as it is well-characterized and studied with good experimental models.<sup>3,4</sup>

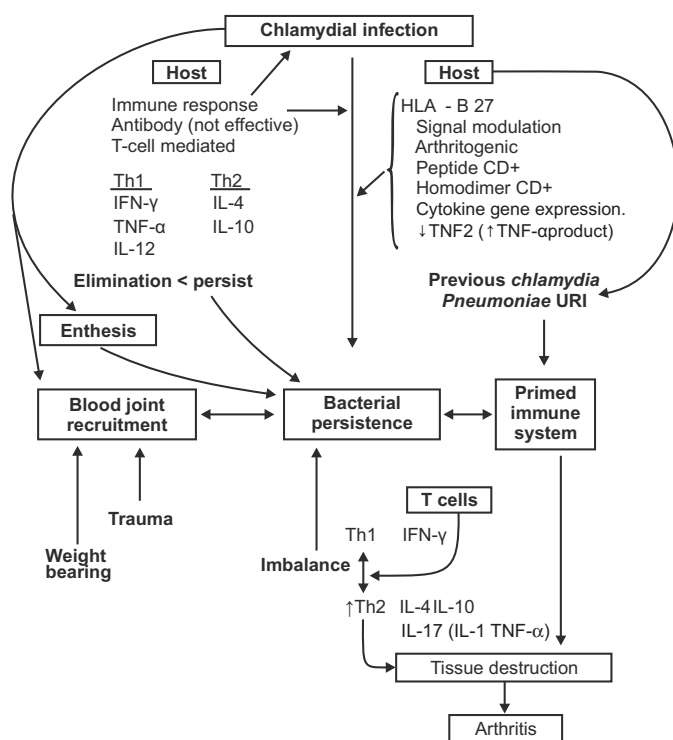
The key to the development of arthritis and enthesitis is the persistence of the organism in the host<sup>3,4,18,35,36</sup> (Fig. 65.9). Several factors contribute to this including the genetic constitution of the host, the genes expressed by the organism, quality of the immune response to the infection, previous exposure to the same or related organisms, the structure of the enthesis, blood joint recruitment, and the reaction that the persistence generates.

HLA B 27 is important, but not crucial, in the development of reactive arthritis.<sup>4</sup> Only 50–60% of patients with chlamydia-related reactive arthritis are positive but those with severe disease are more likely to be positive. Thus it probably contributes more to the severity of inflammation than the actual initiation. It has a role to play in the modulation of the initial signals that promote bacterial persistence rather than elimination.<sup>26</sup> It is also believed to play a part in the possible presentation of an arthritogenic peptide to CD8+

cells initiating a sequence of responses.<sup>4</sup> Although HLA B 27 itself traditionally works through the CD8+ cells being a MHC Class I molecule, its homodimer (with an unpaired cysteine moiety) may allow it to configure itself like a MHC Class II molecule and initiate a CD4+ response.<sup>4</sup> The reactive arthritis related to chlamydia, campylobacter, *Clostridium difficile*, salmonella, shigella, and yersinia is HLA B 27 dependant while that related to neisseria, ureaplasma, vibrio, staphylococci, streptococci, leptospira, brucella, mycobacteria, and hafnia is not.<sup>37</sup> Several other genes play a role in the development of ankylosing spondylitis and some of them may also play an important role in the development of reactive arthritis.

The host immune response to chlamydial infection results in the development of an antibody that may have a role in the prevention of future transmucosal infection. Further, previous exposure to an organism of the same species probably results in the priming of the immune system in a manner that promotes persistence over elimination. Specifically, the host T cell response is more Th2 (IL 4 and IL 10 driven)<sup>3,25</sup> unlike the Th1 response that is driven by interferon-gamma, tumor necrosis factor-alpha and IL 12, which favors the elimination of bacteria. The priming of the immune system to react in this way is attributed to previous exposure to respiratory chlamydial infection. Frequent exposure promotes the development of the Th2 response that allows the Chlamydia to survive in cells. Additionally, *C. trachomatis* heat shock protein 60 (CT-Hsp60) cross reacts with that of *C. pneumoniae*.<sup>3</sup> Persistent *C. trachomatis* infection may allow the release of CT-Hsp60 from infected cells and the subsequent development of anti-CT-Hsp60. Stressed cells infected with *C. trachomatis* may allow the surface expression (sf-Hsp60) of the normally, intracellular, sequestered Hsp60. These antibodies can result in an autoimmune attack, which may be the basis of arthritis, vasculitis, atherosclerosis, and other diseases. Further, immune complexes comprising anti-CT-Hsp60 and circulating Hsp, both chlamydial and human can deposit in the kidney.<sup>38</sup>

The anatomy of the enthesis also favors persistence.<sup>20</sup> The rich blood supply facilitates the lodging of the organisms in close vicinity to the joints. Microtrauma and weight bearing probably magnifies this effect and this may explain why the weight bearing lower limb joints are more often affected.<sup>3</sup> These factors contribute to the recruitment of organisms into the joint, while the Th1/Th2 imbalance allows persistence and tissue destruction. Synovial fluid levels of interferon-gamma and tumor necrosis factor-alpha, which favor bacterial elimination are relatively low in patients with reactive arthritis compared to rheumatoid arthritis while those of Th2 cytokines, IL 4, IL 10, and IL 17 are high.<sup>3</sup> Evidence of chlamydial persistence in the synovial membrane is available in the form of demonstration of the elementary bodies by immunofluorescence and reticulate bodies by electron microscopy.<sup>39</sup> The transcriptional activity of the organism, suggesting active replication, has been shown by demonstration of mRNA and DNA.



**Fig. 65.9:** Diagrammatic representation of the pathogenesis of reactive arthritis related to chlamydial infection. Important host factors include the genetic constitution, the immune response to the infection and previous exposure to similar organisms. The interaction between the immune response and genetic factors favors bacterial persistence and the development of enthesitis. The imbalance between the Th1 and Th2 responses in the presence of a primed immune system facilitates tissue inflammation, destruction and the development of arthritis.



There is scientific evidence to support the claim that patients suffering from Chlamydia-related reactive arthritis mount immune reactions that favor the intracellular persistence of the organism over its elimination. This phenomenon permits the recruitment of infected material to the enthesis and promotes the development of an immunologically maintained inflammatory cascade that results in damage.

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# section **xiii**

## HIV INFECTION AND AIDS

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# Human Immunodeficiency Virus: Biology and Natural History of Infection

Sunil K. Arora • R.S. Paranjape  
• Srikanth Tripathy • Ajay Wanchu

## Introduction

In this chapter is discussed the biology of human immunodeficiency virus (HIV) the causative agent of Acquired Immunodeficiency Syndrome (AIDS), the natural history of HIV infection, its classification, various stages in course of the disease.

It is well-established now that untreated HIV disease progresses relentlessly in almost all infected persons, from a clinically silent infection to severely damaged immunologic function resulting in the AIDS.<sup>1</sup> Following infection, the time before the onset of clinical disease varies from months to years. The duration is influenced by many different factors which may be primarily host related like the age and genetic makeup of the individual, but not by gender or mode of acquisition of the virus.

The disease, if left untreated, leads to death over a median period of about 10 years. However, the time it takes to cover this spectrum varies greatly ranging from one year or less in some patients, to a still unknown upper limit in others. This upper limit has reached nearly 20 years in a few individuals called “long-term non-progressors.” Eventually, it causes death in most people. Various clinical syndromes may occur during the course of HIV disease. Interaction between the host, HIV and environmental factors may determine the course of the disease, clinical manifestations and the rate of disease progression in each individual.

This chapter primarily addresses infection with HIV-1, although HIV-2 is occasionally discussed.

## The Virus

The Retroviridae are a large family of viruses that are associated with many diseases including malignancies, wasting diseases, neurological disorders and immunodeficiencies. Despite the variation in their interaction with the host, all retroviruses are similar in virion structure, genome organization, and mode of replication. A retrovirus is classified as a virus that attaches itself to the host cell and transcribes its viral RNA genome into cellular DNA. The result is the host cell and the virus become one, making it difficult for the normal immune response to combat it. Further,

instead of killing the cell almost immediately after injecting its genetic material, as is the case with many DNA viruses, the retrovirus is able to live as part of the host for an extended period of time. Thus the persons infected with a retrovirus might live for some time without experiencing any strong symptoms and then suddenly find themselves completely overwhelmed. This is the case with the HIV. Only after a long period of incubation do the symptoms of AIDS manifest themselves. The history of retroviruses began in 1908 with the discovery of a filterable transmissible agent associated with disease in chickens.<sup>1</sup> In the next few decades, significant research was carried out on murine leukemia viruses. In 1970, the reverse transcriptase enzyme present in retroviruses was discovered by two different scientists independently (David Baltimore and Howard Temin).<sup>2,3</sup> In 1980, Robert Gallo and his colleagues reported the isolation of the first human retrovirus, which they named Human T-lymphotropic virus or HTLV-1 due to its tropism for T lymphocytes.<sup>4</sup> So far, two evolutionary distinct groups of human retroviruses have been found: (i) the leukemia virus (HTLV-I and HTLV-II), and (ii) the HIVs (HIV-1 and HIV-2). The HIV-1 and HIV-2 viruses were isolated in 1983 and 1986, respectively.<sup>5-7</sup> Retroviruses have been traditionally divided into three subfamilies based on their pathogenicity, that is, *Oncovirinae*, *Lentivirinae*, and *Spumavirinae*. Their classification is given in the Table 66.1.<sup>8</sup>

## Origin of HIV

Korber et al.<sup>9</sup> used phylogenetic analysis in combination with known sampling dates to estimate the year of origin of the HIV-1 group of viruses, which are the cause of the main AIDS pandemic. By the time HIV-1 and HIV-2 were detected in the 1980s, several separate and independent HIV lineages were found to be already causing infections in human populations in Africa.<sup>10</sup> HIV appears to have been transmitted to human beings from at least two different non-human primates infected with simian immunodeficiency viruses (SIVs). The HIV isolates that were transmitted from chimpanzees are known as HIV-1 and those transmitted from sooty mangabey monkeys are known as

**Table 66.1:** Classification of Retroviruses

Subfamily	Group	Examples
Oncovirinae	Avian leukosis sarcoma	Rous sarcoma virus (RSV) Avian myeloblastosis virus (AMV) Avian erythroblastosis virus (AEV) Rous associated virus (RAV)-1–50 RAV-O
	Mammalian C type	Moloney murine leukaemia virus (Mo-MLV) Harvey murine sarcoma virus (Ha-MSV) Abelson murine leukaemia virus (A-MLV) AKR-MuLV Feline leukaemia virus (FeLV) Simian sarcoma virus Reticuloendotheliosis virus (REV) Spleen necrosis virus (SNV)
	B type viruses	Mouse mammary tumor virus (MMTV)
	D type viruses	Mason-Pfizer monkey virus (MPMV) “SAIDS” viruses
	HTLV-BLV group	Human T cell leukaemia (or lymphotropic) virus (HTLV) Bovine leukaemia virus (BLV)
Lentivirinae	Lentiviruses	HIV 1 and 2 Simian immunodeficiency virus (SIV) Feline immunodeficiency virus (FIV) Visna-maedi virus Equine infectious anemia virus (EIAV) Caprine arthritis-encephalitis virus (CAEV)
Spumavirinae	“Foamy” viruses	Simian foamy viruses (SFV)

HIV-2. HIV-1 is most closely related to SIVcpz isolated from the chimpanzee subspecies *Pan troglodytes troglodytes*.<sup>11–13</sup> The most diverse forms of HIV-1 are found in the geographic region corresponding to the region where *Pan troglodytes troglodytes* is found in west equatorial Africa.<sup>14,15</sup> HIV-1 and SIVcpz sequences are closely related phylogenetically, suggesting that there are shared viral lineages in humans and chimpanzees. Similarly, HIV-2 is most closely related to SIVsm natural infection in sooty mangabey monkeys. The natural range of sooty mangabey monkeys overlaps the geographic region where the most diverse HIV-2 viruses have been identified. HIV-2 and SIVsm sequences are closely related in phylogenetic tree analysis.<sup>11–13</sup> It is interesting that HIV-2 does not kill sooty mangabeys, and has a less virulent course in humans, which suggests it evolved much earlier than HIV-1. Analysis of sequence data over the last few years indicates that the last common ancestor of the HIV-1 probably originated around 1930.<sup>9</sup>

There was a marked industrial and economic growth in central African cities such as Kinshasa and Brazzaville in the early part of the 20th century. During this century, easy availability of guns made it easier for man to hunt chimpanzees for their meat.

Increased reliance on chimpanzee meat and changes in hunting/ butchery practices resulted in increased risk of humans coming in contact with chimpanzees. This probably resulted in HIV adapting to humans and causing infection in those who came in contact with chimpanzees and their biological products.<sup>16,17</sup> Subsequently, during the later part of the 20th century, widespread use of air travel made it easier for the spread of HIV to the different regions of the world.

## Virus Structure

HIV comprises a nucleoprotein core surrounded by other protein coats (Fig. 66.1). Under the electron microscope, it appears as a central electron dense core region surrounded by an envelope. On its outer surface is a lipid bilayer containing surface (gp120) and transmembrane (gp41) envelope glycoproteins. The gp120 contains viral determinants that bind to the receptor present on the host cell surface. gp41 contains the transmembrane and cytoplasmic domains that anchor the gp120 onto the surface of the viral lipid layer.

The nucleoprotein core of the virion comprises of two copies of the viral genomic RNA (positive strands, which are identical) and associated RNA molecules, together with *gag* and *pol* protein products, i.e., the nucleocapsid (NC) protein, the capsid (CA) protein and viral enzymes integrase, protease (PR) and reverse transcriptase (RT). The matrix (MA) *gag* protein lines the inner surface of the lipid bilayer.

The capsid (CA) *gag* protein forms the icosahedral viral core. It is hydrophobic and is the major internal structural feature of the virion, that is, the shell of the viral core. Mutations in the CA protein may result in elimination of virus assembly during the late stage of viral replication.

The nucleocapsid (NC or p9) *gag* protein is a small basic protein found in association with viral genomic RNA. It is usually phosphorylated on serine residues, which may be an important determinant for viral assembly. A pair of zinc-finger motifs in the NC protein mediates binding to a region near the 5' end of the viral RNA, which is known as the packaging signal.

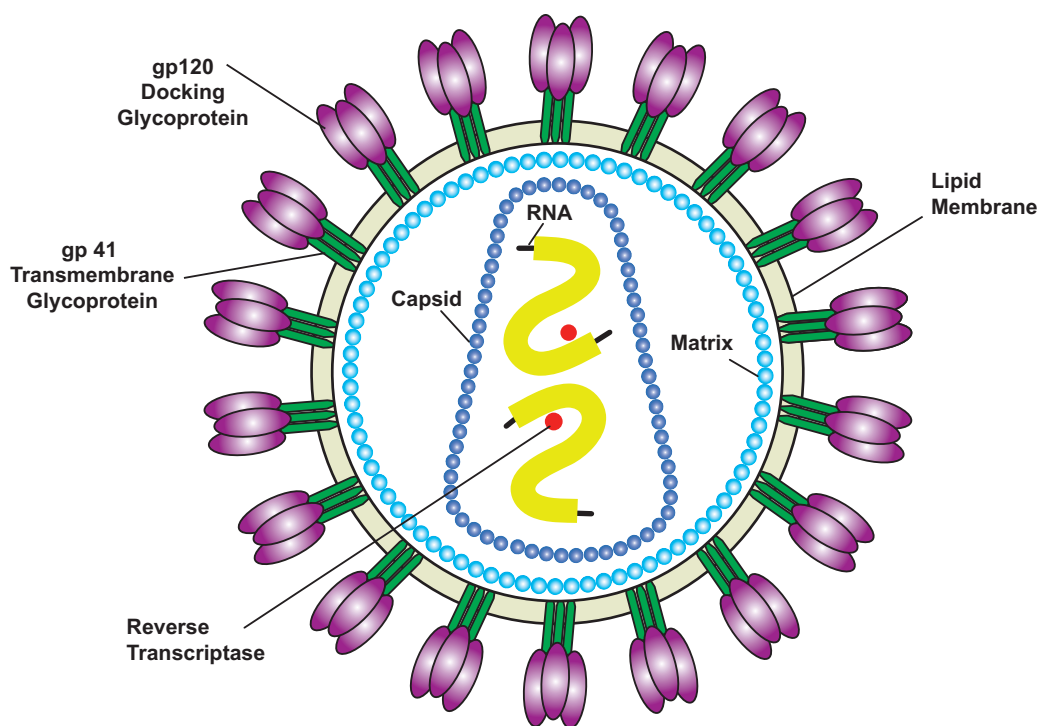
## ENZYMES IN HIV VIRION

The *pol* gene codes for the viral enzymes reverse transcriptase, integrase, and protease.

## Reverse Transcriptase

The primary *pol* product is cleaved by the virion protease to yield the amino-terminal RT peptide and the carboxy-terminal IN (or integrase) protein. The RT peptide has activities necessary for DNA synthesis, which include RNA and DNA directed DNA polymerase, ribonuclease H, and some other nucleolytic activities. The viral polymerase (reverse transcriptase enzyme or RT) is an error-prone enzyme and lacks proof-reading capacity, which results in an error frequency that has been estimated to  $3.4 \times 10^{-5}$  during the reverse transcription.<sup>18</sup> This corresponds to





**Fig. 66.1:** Diagrammatic representation of human immunodeficiency virus structure. *Source:* [www.niaid.nih.gov/factsheets/howhiv.htm](http://www.niaid.nih.gov/factsheets/howhiv.htm).

approximately one new nucleotide substitution per genome per replication cycle.<sup>19</sup> The reverse transcription results in formation of a variety of HIV-1 quasispecies that can have altered cell tropism and drug resistance patterns that can escape the neutralization by the host immune system.

### Integrase

After the viral genomic RNA is reverse transcribed into viral DNA by the reverse transcriptase enzyme it is transported to the host cell chromosomal DNA to form the provirus. This step requires the activity of the viral IN (integrase) protein. The site of integration of the retroviral DNA into the host chromosomal DNA is usually random, although some target sites may be preferred.

### Protease

HIV-1 protease (HIV PR) is essential for the life cycle of HIV. HIV PR cleaves newly synthesized polypeptides at the appropriate places to create the mature protein components of an infectious HIV virion. Without effective HIV PR, HIV virions remain noninfectious. Thus, mutation of HIV PR's active site or inhibition of its activity disrupts ability of the HIV to replicate and infect additional cells, making HIV PR inhibition the subject of much successful pharmaceutical research. In fact the protease inhibitors were "designed" from a detailed knowledge of the structure of HIV PR.

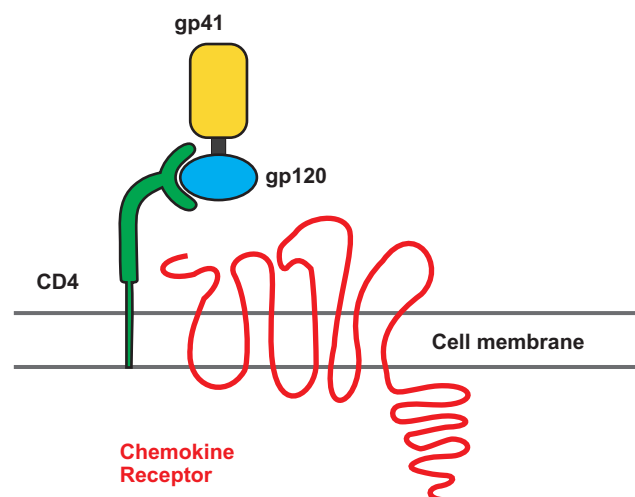
### Envelope Proteins

The *env* gene encodes for a 160 KD precursor glycoprotein composed of 850 amino acids, which is cleaved by an endopeptidase into two glycoproteins, viz gp120, and gp41. There are four highly conserved regions/domains (C1–C4) interspersed with regions of high variability (V1–V5) in the gp120 protein. It is the high degree of variability in the envelope gene, which makes it problematic to prepare a vaccine that will protect against all strains of HIV-1.

### HIV Receptors and Coreceptors

Although HIV is one of the most recently discovered retrovirus, CD4 was the first retrovirus receptor to be identified (Fig. 66.2). The cluster of differentiation (cluster of designation) (often abbreviated as CD) is a protocol used for the identification and investigation of cell surface molecules present on white blood cells. CD molecules can act in numerous ways, often acting as receptors or ligands (the molecule that activates a receptor) important to the cell. A signal cascade is usually initiated, altering the behavior of the cell. Some CD proteins do not play a role in cell signaling, but have other functions, such as cell adhesion.)

In HIV-1 infected adults, the CCR5-Δ32 and CCR2-64I alleles have been associated with a delay of 2 to 4 years in progression to AIDS. In HIV-1 infected children, the presence of the CCR2-64I allele is associated with a delay in the development of AIDS and death. The SDF-1 mutant allele tends



**Fig. 66.2:** Binding of gp120 and gp41 of HIV-1 with CD4 and chemokine receptor on surface of cell. However, expression of CD4 receptor on the cell surface is not enough to allow HIV entry into the cells; for example, HIV-1 cannot infect mouse cells that have been engineered to express CD4.<sup>20</sup> HIV-1 uses several coreceptors for cell entry besides the CD4 receptor. Chemokine receptors (CCR-5 and CXCR-4) and have been shown to be important coreceptors for HIV infection of macrophages and T-lymphocytes, respectively.<sup>21</sup> Allelic variants for the CCR 5, CCR 2, and stromal derived factor, SDF-1, ligand for the CXCR-4, have been recently identified.

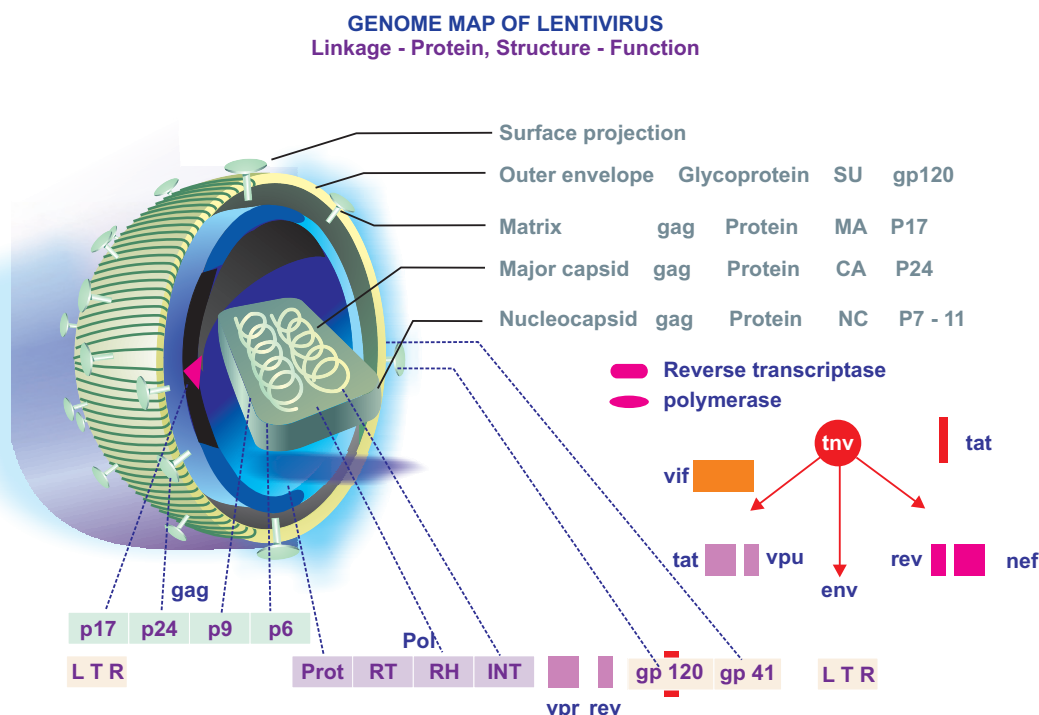
to accelerate disease progression and death. Among SDF-1 3'A carriers, heterozygotes developed AIDS in almost half the time than SDF-1 'Wild' type homozygotes. Moreover, children with

an SDF-1 3'A allele tend to progress to death more rapidly than the wild-type group.

## Structure and Expression of the HIV-1 Genome

The proviral DNA form of the HIV-1 genome consists of 8.5–9 kb of protein coding information, flanked on either side by a pair of identical long terminal repeats (LTRs) (Fig. 66.3). The coding portion encodes for at least 9 recognized genes. These are the virion structural genes (*gag*, *pol*, and *env*), the regulatory genes (*tat*, *rev*, and *nef*), and the accessory genes (*vpu*, *vpr*, and *vif*). The genomic structure of HIV-2 is similar to that of HIV-1 but instead of *vpu*, there is the *vpx* gene in HIV-2.

Transcription of the provirus is controlled by a single promotor in the 5' LTR region and gives rise to a 9 kb primary transcript containing all nine genes. This primary transcript can be either packaged as such into virion particles to form the viral RNA genome or can be spliced into various mRNAs specifying the individual gene products. The primary HIV-1 transcript contains at least four donor (5') and six acceptor (3') potential splice sites.<sup>22</sup> HIV-1 mRNAs fall into three size classes, each with specific functions. The unspliced 9 kb primary transcript that can be packaged into virions or serve as mRNA for *gag* and *pol* or a heterogeneous class of partially spliced mRNA, which code for *env*, *vif*, *vpu*, and *vpr* proteins and for a single exon form of *tat*. Each of these mRNAs is 4–5 kb long. Additionally, another heterogeneous class of viral mRNA, each about 2 kb long and spliced at all potential splice sites is expressed. These codes for viral proteins *rev*, *nef*, and the two exon forms of *tat* (Table 66.2).



**Fig. 66.3:** Diagrammatic representation of the structure of HIV-1.

**Table 66.2:** Important Features of the HIV Genome

Gene/Protein	Regulation	Function
<i>env</i>	Structural	Codes for outer protein coat gp160 (then a protease enzyme splits it into gp120 and gp41)
<i>gag</i>	Structural	Encodes internal proteins (p17, p24, p7, and p9: the nucleocapsid core)
<i>pol</i>	Structural	Encodes the HIV core: p7, p9, RNA genome, reverse transcriptase, ribonuclease, integrase, protease
<i>tat</i>	Positive regulatory	Trans-activator of transcription. Could hasten viral protein production of proviral genome several thousand times. Up-regulates <i>rev</i> , <i>nef</i> , and itself
<i>nef</i>	Negative and positive	“Negative Regulation Factor”. Reduces the rate of RNA initiation (prevents proviral DNA from making more HIV proteins). Also negatively regulates <i>tat</i> and <i>rev</i> . Increase in <i>nef</i> suppresses viral replication. Many HIV strains have defective <i>nef</i> and may sustain latency period
<i>rev</i>	Positive/negative	“Regulator of Expression.” Acts as a genetic switch Prevents RNA expression, the more <i>rev</i> , the more full-length RNA is present and thus the greater amount of expression of <i>env</i> proteins. Downregulates <i>tat</i> and itself
<i>vpr</i>	Weak positive	Transcriptional activator. Moderately stimulates LTR
<i>vpu</i>	Negative?	Not found in HIV-2. If <i>vpu</i> is defective, viruses replicate more quickly Suppresses CD4/ <i>env</i> interactions in the cell
<i>vif</i>	Infectivity	Encodes “virion Infectivity Factor.” Increases the infectivity of HIV. Increases efficiency of cell-to-cell (possibly human-to-human?) transmission

During the early phase of HIV infection, only the fully spliced regulatory mRNAs can be detected in the cytoplasm of the infected cell.<sup>23</sup> Cytoplasmic expression and subsequent translation of the structural mRNAs leading to the production of virions occurs only late in the viral life cycle in response to the viral regulatory protein *rev*.<sup>24</sup> The regulatory proteins *tat*, *rev*, and *nef* proteins together act to either up regulate or down regulate the rate of HIV viral replication in the infected host cell.

The *nef* gene has been detected in all known retroviral genomes. A well-established function of *nef* is the down regulation of CD4, which is the primary receptor for HIV.<sup>25,26</sup> *nef* acts by inducing CD4 endocytosis resulting in its degradation in lysosomes.<sup>27</sup> Some studies have revealed that deletion in the *nef* gene could alter the progress of disease in a HIV infected individual.<sup>28</sup> The *nef* genes of HIV and SIV are dispensable *in vitro* but are essential for viral spread and disease progression *in vivo*. *nef* has been found to be necessary for the maintenance of high viral loads and for the development of AIDS in macaques.<sup>29</sup> A *nef* containing HIV-1 molecular clone induced severe depletion of human thymocytes in immunodeficient (SCID) mice containing human lymphoid tissues (SCID—hu) within 6 weeks of infection but a *nef* deleted HIV-1 did not.<sup>30</sup>

## Replication Cycle of HIV

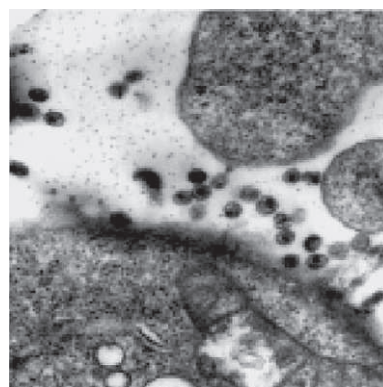
Briefly, the HIV replication cycle can be divided into two phases. The first phase involves the interaction between viral envelope proteins and specific host cell receptors (CD4 and CCR5/CXCR4) followed by fusion of viral and cell membranes, and the entry of the virion core into the target cell cytoplasm. Synthesis of double-stranded DNA by reverse transcription using the single-stranded RNA genome as template is followed by transport of the DNA associated with the virion proteins to the nucleus of the cell and the

integration of the viral DNA into the host chromosomal DNA using the integrase enzyme to form the provirus.

The second phase involves the synthesis of viral RNA by RNA polymerase II using the integrated provirus as the template, followed by processing of the transcripts of the HIV genomic RNA as well as mRNAs for the production of the spliced and unspliced viral mRNA transcripts that encode the regulatory and structural viral proteins. Subsequently, assembly of the precursor structural proteins along with genomic length RNA and budding of the virion particles from the host cell surface takes place along with maturation of the precursor polyproteins to form the infectious viral particle (Fig. 66.4).

## Cell-Surface Binding of HIV

The HIV infection starts with the attachment of HIV by way of the gp120 protein to the CD4 target cell. Virus entry into



**Fig. 66.4:** Emergence of virions from the host cell (electron micrograph).



cells results from the fusion of viral and cell membranes, a process that depends on binding of virus *env* proteins to specific host-cell surface receptors. The CD4 receptor for HIV is composed of four extracellular immunoglobulin (Ig)-like domains and is expressed at the surface of a subset of T lymphocytes and some macrophages.<sup>31</sup> The virus can also infect several cell types of glial and neuroblastoma cell lines<sup>32,33</sup> (Table 66.3) in a manner that is consistent with direct fusion between viral and cell surface membranes.<sup>34</sup> This process is believed to be driven initially by conformational changes in *env* following CD4 binding that expose fusion peptide virus domains located at the amino terminus of gp41.<sup>35</sup> Other possible modes of binding to cells include the binding of antibody-coated viruses to Fc receptors on the surface of macrophages, a process that might explain antibody-mediated enhancement of virus infection, and the high-affinity binding between virus and host cells. The post-binding events required for HIV-1 and cell membrane fusion are less well-understood.

## Reverse Transcription

The reverse transcription pathway generates a linear DNA copy of the viral RNA genome. This step occurs inside a viral nucleoprotein complex and requires the coordinated activities of reverse transcriptase (RT), an RNA and DNA dependent DNA polymerase.<sup>36</sup> The single most important feature of HIV-1 that makes it a difficult target for therapeutic intervention is the high

degree of nucleotide sequence variation between different viral strains.<sup>37</sup> This variability partly reflects the poor fidelity of RT, because it lacks a 3'-5'-exonuclease proofreading activity. Up to 10 incorrect bases may be incorporated during each round of HIV-1 replication.<sup>38</sup> The mutations incorporated by retroviral RTs include amino acid substitutions, 1/+1 frameshifts, and deletions of nucleotide sequence.<sup>39</sup> Reverse transcription generates diverse viruses that can have altered cell-type tropisms, viral "fitness," escape from protective immunity, most commonly, drug-resistance, even before treatment.

## Integration of Viral DNA into Cellular Genomic DNA

The nuclear viral complexes serve as the machines that integrate viral DNA into host cell chromosomal DNA to form a provirus. This step is critically dependent on the activity of the viral integrase enzyme.<sup>40</sup> Retroviral DNA can be integrated into the host genome at a large number of essentially random sites.<sup>41</sup> Integrated retroviral DNA is called "provirus." HIV provirus can survive for years without expression in lymphocytes in a "resting"/"latent"/"dormant" state, where it appears to be safe from immune attack or antiviral drugs.

## Viral Protein Expression

The expression of viral genes needs the collaborative activities of the host cell transcription machinery (RNA polymerase and

**Table 66.3:** Cell Types Affected by HIV

Name	Structure/Function	Impairment in AIDS
<b>CD4+ T-cells</b>	Helper cells that recognize antigen presented by APCs (antigen presenting cells) in context of major histocompatibility complex (MHC) Class II	Functional (IL-2 production) and proliferative decline over time
<b>CD8+ T-cells</b>	Cytotoxic T-cells that recognize antigen presented by APCs in context of MHC Class I. Kill infected cells	Subsets influenced variously; counts increase over time. IL-12 levels are up at first in HIV, but subsequently decline
<b>Memory T-cells</b>	T-cells with quickened response to second exposure of same antigen; these cells express CD 45 receptor (CD45 RO are so-called "naive" cells)	CD 45 RA/RO drop
<b>B-cells</b>	Identify extracellular antigens and secrete antibody in plasma	Hypergammaglobulinaemia
<b>Monocytes/-</b>	cells	HIV infects these cells directly; does not appear to inhibit cytokine production, however
<b>Macrophages</b>	Antigen presenting cell (APC)	
<b>Langerhans/dendritic cells</b>	Antigen presenting cell (APC). Langerhans cells in skin can migrate into lymph system becoming dendritic cells	Impaired function
<b>Follicular dendritic cells</b>	Role as APC in capturing infectious agents on skin and mucous membranes in tree-like branches extending out from cell body	HIV can use these cells to gain access to the body through undamaged mucous membranes, other roles in pathogenesis still unclear
<b>Natural killer (NK) cells</b>	Assist in killing cells marked or coated by antibodies	Impaired function in HIV
<b>Kupffer cells</b>	Macrophages within liver	Infected by HIV
<b>Epithelial cells</b>	Skin primary structural component; lining of blood vessel walls and gut	Some types of epithelial cells can be infected by HIV, also, around brain, gut, and cervical area. Destruction of epithelial cells separating blood-brain barrier
<b>Sperm</b>	Male germ cell; motile cells	HIV can infect these cells; HIV appears to "ride" within sperm "head"
<b>Ova</b>	Female egg cell	Protected by amniotic sack

transcription factors) and viral regulatory proteins (*tat* and *rev*). The spliced viral mRNA transcripts give rise to *env* and to the regulatory *tat*, *rev*, and *nef* proteins. Unspliced transcripts encode the Pr55 *gag* and Pr160 *gag-pol* fusion proteins and also serve as genomic RNA packaged into newly assembling virus particles.<sup>42</sup>

## Virus Assembly

Newly synthesized HIV core proteins, enzymes and RNA gather just within the cell membrane and at the same time the envelope proteins aggregate within the membrane. An immature viral particle forms and pinches off from the cell and acquires an envelope that includes both the cellular and HIV proteins from the cell membrane.

## Envelope Proteins

Retroviral *env* proteins are synthesized within the endoplasmic reticulum (ER) of infected cells and are transported to the cell surface by the host-cell secretory pathway. Within the ER, monomers of gp160, the precursor HIV *env* protein, associate with molecular chaperone (BiP), before folding and oligomerization.<sup>43</sup> Once *env* is expressed in the infected cell, synthesis of cell-surface CD4 is down regulated, so that the cell becomes resistant to superinfection. During or soon after budding, retroviral particles mature when the *gag* and *gag-pol* polyproteins get cleaved into mature protein products by viral protease. This cleavage is an essential step in the maturation of retrovirus particles, because mutations in protease lead to production of non-infectious virus particles that contain uncleaved core proteins.<sup>44</sup> The mature virions that are released from the cell are competent to restart the replication cycle in other target cells.

## Early Events in HIV Infection

HIV is transmitted primarily through sexual contact, and hence genital mucosal surfaces are the portal of entry for HIV virus. Mucosal surfaces, including the oropharynx, rectum, and genital mucosa, are the sites rich in Langerhans cells—dendritic cells that trap antigens and virus particles. Dendritic cells trap the antigen through the receptor DC-SIGN which is instrumental in transporting the virus to the draining lymphoid tissue where the virus infects CD4 lymphocytes. The DCs and CD4 cells of mucosal surface may also get infected and actively produce the virus. Within hours of exposure of genital mucosa to the virus, multiplying virus may be detected in the draining lymph nodes. When female macaques were experimentally inoculated with SIV through the intravaginal route, the virus was first found in association with mucosal Langerhans cells.<sup>45</sup> Infection of dendritic cells and T cells in the genital mucosa can be detected within 18 hours after inoculation.<sup>46</sup> Contact between SIV and the vaginal mucosa for as little as 2 hours is sufficient to result in infection. Within a few days, the virus can be detected in neighboring lymphocytes and monocytes and then in the regional lymphoid tissues. Subsequently, primary viremia leads

to widespread dissemination of the virus, seeding of lymphoid tissues throughout the body resulting in acute HIV infection.

## Virus Multiplication and Establishment of Pool of Latently Infected CD4 Cells

During the time of primary viremia of HIV infection, a large numbers of infected cells in the peripheral blood and high titers of infectious virus in the plasma can be detected. These include titers as high as  $10^7$  HIV particles/ml.<sup>47</sup> These titers decline rapidly as effective virus-specific immunity develops in the host. Virus often becomes undetectable in the plasma, and the number of infected cells in the circulation may decline to less than 1 in 1 million peripheral blood mononuclear cells.

Virus titers in the blood begin to decline even before neutralizing antibodies can be detected suggesting that some other immunologic mechanism must be responsible for the initial control of virus replication. There is evidence that antibody dependent cellular cytotoxicity and HIV-specific cytotoxic T lymphocytes appear before the neutralizing antibodies become detectable.<sup>48,49</sup> The role of innate immune responses in initial control of virus multiplication is also being very actively explored. At one stage even though the virus appears to have disappeared from the blood, HIV replication continues unabated in lymphoid tissues. Studies of lymph node biopsies, using nucleic acid hybridization techniques that detect HIV RNA and DNA sequences in lymphoid tissues in patients in the early stages of HIV infection, have demonstrated active virus replication in the lymph nodes even during the clinically latent stage of infection.<sup>50</sup> These observations prove that HIV is never truly latent but instead causes a chronic active infection with continuous virus production at all stages of disease. Recent reports indicate that Gut Associated Lymphoid Tissue is a major site where the virus multiplies leading to the destruction of CD4 cells; paradoxically this co-exists with immune activation that sustains HIV infection. HIV preferentially infects memory CD4+ lymphocytes. Activated CD4+ cells are more easily infected by HIV-1 since they express higher levels of chemokine receptors that serve as coreceptors for the virus. Further, activated cells express high levels of nuclear transcription factors, which are required for expression of HIV-1 genes from proviral DNA. Thus, most of the infected activated CD4+ cells are productively infected and die within a few days. Resting CD4+ cells are occasionally infected, and some infected activated cells may revert to a resting state. These cells constitute the reservoir of latently infected resting CD4+ cells. It is during this period that the latent reservoir is established. This HIV reservoir in the resting CD4+ cells is refractory to antiretroviral treatment and immune mechanisms.

Within the lymph nodes and related organs, large amount of virus gets trapped within networks of specialized cells called follicular dendritic cells (FDCs). These are located in the germinal centers of the lymph nodes. They trap invading pathogens (including HIV) and hold them until B cells become available to initiate an immune response. B cells are followed by CD4+

T cells, which reach the germinal centers to assist B cells. CD4+ T cells, the primary targets of HIV, probably become infected in large numbers as they encounter HIV trapped on FDCs. HIV trapped on FDCs remains infectious, even when coated with antibodies. Once infected, it is possible for the CD4+ T cells to leave the germinal centre and infect other CD4+ cells that collect in the lymph node surrounding the germinal centre. Over years, even when little virus is readily detectable in the blood, significant amounts of virus accumulate in the germinal centers, both within infected cells and bound to FDCs. In and around the germinal centers, numerous CD4+ T cells get activated by the increased production of cytokines such as tumor necrosis factor (TNF)- $\alpha$  and interleukin (IL)-6, possibly secreted by B cells. Activation allows uninfected cells to be more easily infected and increases replication of HIV in already infected cells.

## Factors Influencing HIV Disease Progression

### HOST FACTORS

In adults, HIV infection progresses more rapidly in older people. Studies of adult hemophiliacs suggest that their progress to late symptomatic disease is faster than that of hemophiliac children. Transfusion recipients over 60 years of age had more rapid disease progression than their younger counterparts.<sup>51</sup> However, age was not an independent predictor of disease progression in a study on intravenous drug users,<sup>52</sup> and its significance in disease progression in homosexual men is unsettled.

Gender does not appear to have a major influence on disease progression, although natural history studies of HIV disease in women are lacking and the independent role of gender has not been extensively studied. Ethnicity or race also does not appear to influence disease progression; however, host genotype may be influential.<sup>53</sup> In the US, the incidence of AIDS in lower income groups has been rising since 1987,<sup>54</sup> and is likely to reflect the high prevalence of high-risk behaviors, inequitable access to medical care, and poor utilization of medical resources in these groups.

Approximately 5% of HIV infected patients will remain clinically well without immune deterioration for a decade or more after seroconversion and are known as “long-term survivors” or long-term nonprogressors. A recent study of long-term survivors showed that they have a strong CD8+ lymphocyte response and a broad and strong neutralizing antibody response to HIV-1. There is also evidence that there may be some attenuation of the HIV isolates in this patient group.<sup>55</sup>

### HIV RISK GROUPS

It is possible that HIV seropositive intravenous drug users, who have an increased incidence of pulmonary tuberculosis and serious bacterial infections, are more likely to progress rapidly to AIDS. Poverty and poor access to medical care may largely explain this variation.<sup>56</sup>

### VIRAL AND OTHER COFACTORS

In a study of HIV infected hemophiliacs, those who were cytomegalovirus (CMV) seropositive had a 2–4-fold higher risk of progression to late symptomatic disease than those who were seronegative.<sup>57</sup> This finding suggested that CMV may be a cofactor and the rate of disease progression in seropositive hemophiliacs was equivalent to those of HIV infected homosexuals who are almost universally seropositive for CMV. There is no clinical evidence that Epstein–Barr virus (EBV), human herpes virus 6 (HHV6), and hepatitis B virus act as cofactors in HIV disease. However, along with herpes simplex virus, these agents have all been shown to enhance HIV replication *in vitro*. It has been postulated that *Mycoplasma fermentans* may be a cofactor in HIV infection, but a recent study did not show any evidence for this.<sup>58</sup> Coinfection with both HIV 1 and HIV 2 has been reported but the rate of disease progression with dual infection is unknown. Hepatitis C virus is known to cause rapid progression of HIV disease.

### DEFECTIVE CORECEPTORS

HIV must bind to the surface protein called CD4 receptor in order to infect a cell. Another cell surface protein called “chemokine receptor” is also necessary for efficient HIV entry into the cell. CCR5 is one such coreceptor for which many individuals in the population carry a mutant gene (Delta-32 deletion). This mutation prevents the gene from producing a product that HIV can use as a coreceptor. If the individuals are homozygous for Delta-32, they are at less risk of becoming infected when exposed to HIV.<sup>59–61</sup> However, this protection is not absolute.

### SDF-1 GENE MUTATION

Individuals with the mutation of the gene producing a chemokine called stromal-derived factor 1 (SDF1) may be more resistant to infection. SDF1 is a cytokine that normally binds to the chemokine receptor CXCR4. The mutation may produce a limited level of SDF1, which in turn may affect the ability of HIV-1 to infect cells.<sup>62</sup>

### OTHER POTENTIAL COFACTORS

Some studies found an association between smoking and the more rapid rate of CD4+ lymphocyte loss or more rapid progression to disease. However, it was not supported by other studies.<sup>63,64</sup> Severe malnutrition, of the type observed in the developing countries, may accelerate HIV disease progression.<sup>65</sup> Whether milder forms of malnutrition play any significant role is less clear. Depression, stress, bereavement, and other psychological factors have not been shown to affect disease progression.

## Terminology of Untreated HIV Disease

### PROGRESSIVE GENERALIZED LYMPHADENOPATHY

The progressive generalized lymphadenopathy syndrome is a manifestation of an early stage HIV disease but without having any prognostic significance and specific implications. It must be



differentiated from lymphadenopathy caused by other disease processes, especially infectious diseases and lymphomas.

### AIDS-RELATED COMPLEX

The term AIDS-related complex (ARC) has been abandoned. We now know that the symptoms and signs labeled with the term ARC are manifestations of the middle stage of HIV disease. Hindsight revealed that ARC really means symptomatic HIV disease that does not qualify for the label of AIDS. Because the term ARC does not usefully locate a patient within the long continuum of middle stage disease; it is not useful in clinical management, as a case definition for reporting, or as a definable point for clinical studies.

### Acquired Immunodeficiency Syndrome (AIDS)

This syndrome is the last stage of HIV disease. Centers for Disease Control and Prevention (CDC) has subsequently revised its original case definition published in September 1982<sup>66</sup> to accommodate additional conditions recognized as manifestations of advanced HIV disease.<sup>67–71</sup> The term AIDS signifies the last stage of HIV disease in which immunodeficiency has become profound. However, advanced HIV disease is probably more descriptive. The 1987 CDC definition of AIDS continues to be useful to define an “end point” of HIV disease in clinical research and as criteria for case reporting that helps to quantify the growth of the epidemic of HIV disease. However, the criteria are irrelevant for the medical management of HIV disease, because an individual patient may not meet the criteria for AIDS as defined by CDC.

Following the introduction of highly active antiretroviral therapy; the concept of AIDS, as “end stage” immunodeficiency has become somewhat distorted. Highly active antiretroviral therapy can improve immunological function by boosting the CD4+ count and reducing the incidence of opportunistic infections whilst masking the remaining immune system deficits.

### Classification and Staging

Some system of nomenclature and classification is necessary to describe the progression of HIV disease through its stages in consistent and generally accepted terms. The CDC/World Health Organization (WHO) system that emphasizes the clinical presentation of HIV disease (Table 66.4 a and b)<sup>72,73</sup> is intended for “public health purposes, including disease reporting and surveillance, epidemiological studies, prevention and control activities, and public health policy planning epidemiological data”, but is of limited value for describing the progression of disease in an individual during clinical management or clinical research. Prior to 1996, when HIV RNA assays became widely available, clinicians used a combination of CD4+ counts and clinical signs for estimating stage and prognosis. There is as yet, no widely accepted standard formal system for the clinical staging of HIV disease.<sup>74</sup>

To characterize the disease in an individual, for the purpose of estimating prognosis, planning therapy and establishing criteria for enrolment or end points in clinical trials, the clinician would like to know how far the disease has progressed and how rapidly it is progressing. In untreated HIV disease, the former is currently most usefully indicated by the CD4+ count and the latter by the plasma HIV RNA level, usually termed as the “viral load.”

### Viral Load during HIV Infection: The Set Point

There is continuous viral replication from the time of initial infection until death. About 10 billion HIV virions are produced every day with a half-life of 6 hours in the plasma. CD4+ lymphocytes, which are one of the principal target cells responsible for viral replication, are also produced in high numbers and once infected will have a half-life of about 6 days. The life cycle of HIV infection from entry into one cell to the production of new progeny, which infect new cells, is about 2.6 days. Hence, there is an extraordinarily high level of viral replication, cell destruction and cell replacement.

HIV RNA becomes detectable in patient's blood within weeks of infection and precedes the appearance of HIV antigen and HIV antibodies. Over the following weeks, the level rises to a peak and then stays at a relatively stable level that is referred to as the set point (Fig. 66.5).<sup>75–78</sup> For an individual, this level is set to change relatively slowly over the following months or possibly years. The set point varies in different patients and its magnitude is related to the risk of disease progression. HIV viral load measurement is a major advance in HIV disease management and has two major applications, estimating the risk of progression (the prognosis) (Table 66.5) and monitoring the effectiveness of anti-HIV drug therapy. Studies prove a very strong correlation between the higher HIV viral load and the faster rate of progression of HIV disease.<sup>79–81</sup>

The HIV infected person will progress more or less sequentially through a series of characteristic clinical stages with the progressive depletion of CD4+ lymphocyte counts. The HIV infection can be divided into four stages:

1. Acute seroconversion illness or primary HIV infection
2. Asymptomatic stage of HIV infection
3. Early symptomatic stage of HIV infection
4. Late symptomatic and advanced stage of HIV infection (AIDS).

This clinical staging can be combined with a measure of immunodeficiency such as the total lymphocyte count (more than 2000, 1000–1999, and less than 1000 cells/ $\mu$ L) or, if available, CD4+ or T helper cell count (>500, 200–500, or <200/ $\mu$ L) to produce nine possible HIV stages (Table 66.6).

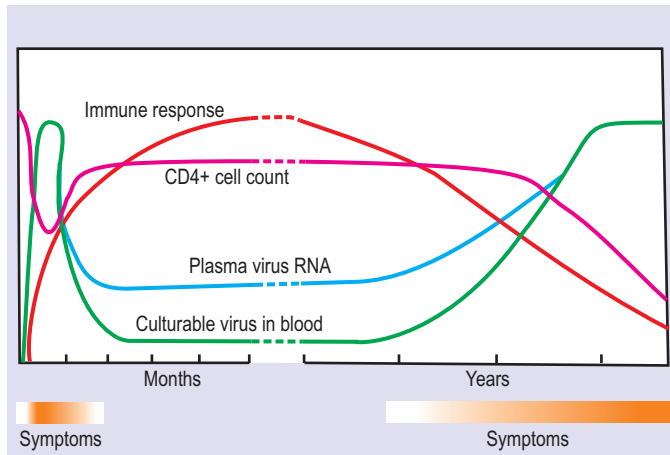
### STAGE 1: PRIMARY HIV INFECTION

Primary HIV infection (PHI) or acute HIV infection occurs before the antibody response. When the latter occurs, up to 90% of people may experience an acute seroconversion illness within 2–4 weeks of exposure. It usually resolves within 2 weeks and

**Table 66.4:** HIV Classification: CDC and WHO Staging Systems (July 2006; updated April 2009)

(a) CDC classification system for HIV-infected adults and adolescents				(b) WHO clinical staging of HIV/AIDS for adults and adolescents	
CD4 cell categories	Clinical categories			Primary HIV infection	
	A Asymptomatic, acute HIV, or PGL	B Symptomatic conditions,# not A or C	C AIDS- indicator conditions*	<ul style="list-style-type: none"> <li>Asymptomatic</li> <li>Acute retroviral syndrome</li> </ul>	
(1) ≥500 cells/μL	A1	B1	C1	Clinical Stage 1	
(2) 200–499 cells/μL	A2	B2	C2	<ul style="list-style-type: none"> <li>Asymptomatic</li> <li>Persistent generalized lymphadenopathy</li> </ul>	
(3) <200 cells/μL	A3	B3	C3	Clinical Stage 2	
Abbreviations: CDC, Centers for Disease Control and Prevention; PGL, persistent generalized lymphadenopathy.				<ul style="list-style-type: none"> <li>Moderate unexplained weight loss (&lt;10% of presumed or measured body weight)</li> <li>Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis)</li> <li>Herpes zoster</li> <li>Angular cheilitis</li> <li>Recurrent oral ulceration</li> <li>Papular pruritic eruptions</li> <li>Seborrheic dermatitis</li> <li>Fungal nail infections</li> </ul>	
CDC classification system: category B symptomatic conditions				Clinical Stage 3	
Category B symptomatic conditions are defined as symptomatic conditions occurring in an HIV-infected adolescent or adult that meet at least 1 of the following criteria:				<ul style="list-style-type: none"> <li>Unexplained severe weight loss (&gt;10% of presumed or measured body weight)</li> <li>Unexplained chronic diarrhea for &gt;1 month</li> <li>Unexplained persistent fever for &gt;1 month (&gt;37.6°C, intermittent or constant)</li> <li>Persistent oral candidiasis (thrush)</li> <li>Oral hairy leukoplakia</li> <li>Pulmonary tuberculosis (current)</li> <li>Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia)</li> <li>Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis</li> <li>Unexplained anemia (hemoglobin &lt;8 g/dL)</li> <li>Neutropenia (neutrophils &lt;500 cells/μL)</li> <li>Chronic thrombocytopenia (platelets &lt;50,000 cells/μL)</li> </ul>	
a) They are attributed to HIV infection or indicate a defect in cell-mediated immunity.				Clinical Stage 4	
b) They are considered to have a clinical course or management that is complicated by HIV infection.				<ul style="list-style-type: none"> <li>HIV wasting syndrome, as defined by the CDC</li> <li><i>Pneumocystis</i> pneumonia</li> <li>Recurrent severe bacterial pneumonia</li> <li>Chronic herpes simplex infection (orolabial, genital, or anorectal site for &gt;1 month or visceral herpes at any site)</li> <li>Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)</li> <li>Extrapulmonary tuberculosis</li> <li>Kaposi sarcoma</li> <li>CMV infection (retinitis or infection of other organs)</li> <li>Central nervous system toxoplasmosis</li> <li>HIV encephalopathy</li> <li>Cryptococcosis, extrapulmonary (including meningitis)</li> <li>Disseminated nontuberculosis <i>Mycobacteria</i> infection</li> <li>Progressive multifocal leukoencephalopathy</li> <li>Candida of the trachea, bronchi, or lungs</li> <li>Chronic cryptosporidiosis (with diarrhea)</li> <li>Chronic isosporiasis</li> <li>Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis)</li> <li>Recurrent nontyphoidal <i>Salmonella</i> bacteremia</li> <li>Lymphoma (cerebral or B-cell non-Hodgkin)</li> <li>Invasive cervical carcinoma</li> <li>Atypical disseminated leishmaniasis</li> <li>Symptomatic HIV-associated nephropathy</li> <li>Symptomatic HIV-associated cardiomyopathy</li> <li>Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)</li> </ul>	
Examples include, but are not limited to, the following:					
<ul style="list-style-type: none"> <li>Bacillary angiomatosis</li> <li>Oropharyngeal candidiasis (thrush)</li> <li>Vulvovaginal candidiasis, persistent or resistant</li> <li>Pelvic inflammatory disease (PID)</li> <li>Cervical dysplasia (moderate or severe)/cervical carcinoma <i>in situ</i></li> <li>Hairy leukoplakia, oral</li> <li>Idiopathic thrombocytopenic purpura</li> <li>Constitutional symptoms, such as fever (&gt;38.5°C) or diarrhea lasting &gt;1 month</li> <li>Peripheral neuropathy</li> <li>Herpes zoster (shingles), involving ≥2 episodes or ≥1 dermatome</li> </ul>					
CDC classification system: category C AIDS-indicator conditions*					
<ul style="list-style-type: none"> <li>Bacterial pneumonia, recurrent (≥2 episodes in 12 months)</li> <li>Candidiasis of the bronchi, trachea, or lungs</li> <li>Candidiasis, esophageal</li> <li>Cervical carcinoma, invasive, confirmed by biopsy</li> <li>Coccidioidomycosis, disseminated or extrapulmonary</li> <li>Cryptococcosis, extrapulmonary</li> <li>Cryptosporidiosis, chronic intestinal (&gt;1 month duration)</li> <li>CMV disease (other than liver, spleen, or nodes)</li> <li>Encephalopathy, HIV-related</li> <li>Herpes simplex: chronic ulcers (&gt;1 month duration), or bronchitis, pneumonitis, or esophagitis</li> <li>Histoplasmosis, disseminated or extrapulmonary</li> <li>Isosporiasis, chronic intestinal (&gt;1 month duration)</li> <li>Kaposi sarcoma</li> <li>Lymphoma, Burkitt, immunoblastic, or primary central nervous system</li> <li><i>Mycobacterium avium</i> complex (MAC) or <i>M. kansasii</i>, disseminated or extrapulmonary</li> <li><i>Mycobacterium tuberculosis</i>, pulmonary or extrapulmonary</li> <li><i>Mycobacterium</i>, other species or unidentified species, disseminated or extrapulmonary</li> <li><i>Pneumocystis jiroveci</i> (formerly <i>carinii</i>) pneumonia (PCP)</li> <li>Progressive multifocal leukoencephalopathy (PML)</li> <li><i>Salmonella</i> septicemia, recurrent (nontyphoid)</li> <li>Toxoplasmosis of brain</li> <li>Wasting syndrome due to HIV (involuntary weight loss &gt;10% of baseline body weight) associated with either chronic diarrhea (≥2 loose stools per day ≥1 month) or chronic weakness and documented fever ≥1 month</li> </ul>					

Source: www.aidsetc.org



**Fig. 66.5:** Virologic and immunologic course of HIV disease. Staging of HIV Infection.

may resemble glandular fever. Rarely, the illness may be quite prolonged and may merge into the later stages of HIV illness. Transient CD4<sup>+</sup> lymphopenia has been seen in the few patients studied.<sup>82</sup> At the time of PHI, there is always a high rate of viral replication leading to a transient rise in HIV viral load and concomitant immunosuppression due to a short-lived fall in the CD4<sup>+</sup> lymphocyte count. Sometimes the illness may be severe

**Table 66.5:** Correlation Between Viral Load and Survival Over Period of Time

HIV-1 RNA (/ml)	HTF-1 RNA (Log <sup>10</sup> )	Median time to AIDS (years)	% with AIDS at 6 years	Median survived (years)	% dead at 6 years
<500	<2.7	>10	5.4	>10	0.9
501–3000	2.7–3.47	>10	16.6	>10	6.3
3001–10,000	3.47–4.0	8.3	31.7	>10	8.1
10,000–30,000	4.0–4.47	5.5	55.2	7.5	34.9
>30,000	>4.47	2.8	80.0	4.4	69.5

with symptoms suggestive of AIDS, for example, oropharyngeal candidiasis and *Pneumocystis jirovecii* pneumonia. Diagnostic confusion as to the stage of HIV infection may arise, which can only be resolved by follow-up of the patient long enough to see the signs and symptoms resolve. HIV antibodies appear, the viral load falls and the CD4<sup>+</sup> count rises. A mild seroconversion illness may be missed if the clinician does not have a high index of suspicion and if a history indicating relevant risk behaviors or factors is not taken into account.

The appropriate diagnostic tests of PHI, which should be carried out on serial blood samples, includes a test for HIV antibodies. If this is negative and a primary HIV infection is suspected, then direct demonstration of viremia is necessary,

**Table 66.6:** Clinical Stages of HIV-1 Disease and Characteristics of Clinical Presentations with CD4<sup>+</sup> Cell Count Range

Stage of HIV disease	Clinical presentation	Usual CD4 <sup>+</sup> cell count/ $\mu$ L	Usual duration
Seroconversion illness/Primary HIV Infection (PHI)/Acute HIV infection	Fever, pharyngitis, rash, fatigue, mucocutaneous ulcers, lymphadenopathy, headaches, meningitis, encephalitis, neuropathies	150–800	3–14 days
Asymptomatic	Lymphadenopathy, headache	>300	2–10 days
Early symptomatic	Recurrent varicella zoster Oral candidiasis Seborrheic dermatitis Psoriasis Skin and nail infections (impetigo, folliculitis, fungal intertrigo, paronychia) Bacterial infections (pneumonia, bronchitis, sinusitis) Unexplained fatigue, fever, sweats, weight loss Diarrhoea Vaginal candidiasis Cervical dysplasia Cervical carcinoma <i>in situ</i> Recurrent pelvic inflammatory disease Tuberculosis	150–500	1–5 years
Late symptomatic	Kaposi's sarcoma Lymphoma <i>Pneumocystis carinii</i> pneumonia Toxoplasmosis Oesophageal candidiasis Cryptococcosis, cryptosporidiosis Recurrent herpes simplex virus HIV-I associated dementia complex Progressive multifocal leukoencephalopathy Tuberculosis	50–200	1–4 years
Advanced	Cytomegalovirus retinitis Cerebral lymphoma <i>Mycobacterium avium</i> complex infection (MAC)	<50	<2 years



using a p24 antigen (insensitive) or PCR. However, this is not available at all centers.

Lymphadenopathy typically appears in the second week of the PHI and may be generalized but preferentially affects the occipital, axillary, and cervical groups. Lymphadenopathy generally subsides in the majority of patients but may not completely resolve. A seroconversion illness associated with HIV-2 infection has also been reported.<sup>82</sup>

Treatment should be directed at alleviating any symptoms. There is considerable interest in the possible use of antiretroviral agents at this time. The virus may be more susceptible to treatment due to the relatively low numbers of virus particles that can replicate. The reduced ability of virus to infect a wide variety of cell types and the enhanced immune response seen in PHI renders the organism much more susceptible to treatment. The treatment could possibly prevent long-term damage to the immune system and delay or even prevent the development of AIDS.

## STAGE 2: ASYMPTOMATIC STAGE OF HIV INFECTION

Most HIV infected adults and children may expect to remain asymptomatic for many years following seroconversion. During this period, there are typically no abnormal findings on physical examination but the laboratory tests, related to HIV infection, are frequently abnormal. About 20–30% of people who develop lymphadenopathy during their seroconversion illness may have persistent generalized lymphadenopathy throughout the asymptomatic stage. Occasionally, people may experience headaches, which can be recurrent or chronic and debilitating in nature.<sup>83</sup>

CD4+ cell counts are usually within the normal range during the initial phase of the asymptomatic period. The rate of decline of the CD4+ cell count has been estimated as 84 cells per year for the first 4 years after seroconversion,<sup>84</sup> but enormous variations may occur among individuals and also within a single individual over time. The time between seroconversion and the development of early symptomatic disease has not been well-defined.

## STAGE 3: EARLY SYMPTOMATIC STAGE OF HIV INFECTION

Following infection with HIV, individuals may be entirely asymptomatic or may simply have enlarged lymph nodes with or without minor symptoms such as tiredness, lethargy, excessive sweating, and aches or pains in muscles or joints. The time between seroconversion and late symptomatic disease has been studied extensively and is estimated to be 11 years for homosexual men, with a possible variation in other HIV groups. Using statistical models, it has been projected that 76% of HIV infected people will develop late symptomatic disease by the year 16 of infection.<sup>85</sup> The rate of HIV-1 disease progression has been estimated to be three to four times greater than that of HIV-2.<sup>86</sup>

Through the early stage of HIV disease, the levels of virus detectable in the peripheral blood often remain low. However, this masks a very rapid rate of virus production and destruction in the lymphoid tissue.<sup>87</sup> The frequently observed generalized lymphadenopathy syndrome is probably a manifestation of this

process.<sup>88</sup> Many patients have painless, stable lymphadenopathy, which in some cases regresses as HIV disease advances, possibly because active HIV replication and immune destruction gradually destroy the architecture of lymph follicles. Anergy to skin testing becomes increasingly probable as the CD4+ count falls below 400/ $\mu$ L, with obvious implications for tuberculosis screening.

Common episodic conditions during this and later stages of disease include herpes zoster, *Candida*, seborrheic dermatitis, skin and nail infections like impetigo, folliculitis, fungal intertrigo, and paronychia along with bacterial infections like pneumonia, bronchitis, and sinusitis. Despite the relative scarcity of severe neutropenia in early HIV infection, bacterial sepsis is a major clinical problem that usually manifests as pneumonia, bacteremia or both. The incidence is 8–20 per 100 person years, depending on factors including location and risk activity. Recurrent herpes zoster is one of the earliest manifestations of symptomatic disease.

Oral candidiasis and oral hairy leukoplakia also occur but may not appear until a year after an episode of herpes zoster. Constitutional symptoms may occur for which no recognized cause is established by routine or specific investigations. These symptoms which include fatigue, fever, sweats, weight loss, and diarrhea occur relatively late in the stage of the disease. The pattern of occurrence and duration of constitutional symptoms varies greatly between individuals and their pathogenesis is likely to be a reflection of ongoing HIV replication and host immune response. Women may suffer from recurrent or persistent vaginal candidiasis. Moderate to severe cervical dysplasia or cervical carcinoma *in situ* are also clinical markers of early symptomatic disease in women. Pulmonary tuberculosis may occur in early or late symptomatic HIV disease.

Neurological manifestations including peripheral neuropathy and subtle manifestations of HIV dementia occasionally appear even in the early part of this period. Symptoms of peripheral neuropathy may persist, worsen, or in some cases, resolve as the disease progresses.

Dysregulation of the immune system leads to the proliferation of antibody producing B cells, hypergammaglobulinemia and occasional manifestations of autoantibody production such as immune thrombocytopenic purpura (although true purpura and bleeding are unusual) and prolonged partial thromboplastin time (lupus anticoagulant). As HIV disease advances and the immune system deteriorates, these manifestations often improve, presumably reflecting the decreasing ability to produce antibodies of any kind.

Isolated lesions of Kaposi sarcoma (KS) as opposed to extensive and rapidly progressive KS, may appear very early in HIV disease (CD4+ count > 500/ $\mu$ L). These early isolated KS lesions do not imply a poor prognosis. Isolated systemic non-Hodgkin lymphoma (NHL) lesions, but not central nervous system NHL, may occur in the middle stages of HIV disease.

Several of these clinical findings have been shown to be useful predictors of progression to late symptomatic disease but not independently of CD4+ cell counts. In one study of cohorts of homosexual men, the 2 years progression to AIDS for men with

herpes zoster, *Candida*, oral hairy leukoplakia, and constitutional symptoms were 25%, 39%, 42%, and 100%, respectively.<sup>60</sup> The predictive significance of the conditions exclusive to women has not been as well characterized as yet.

When the CD4+ count is about 350/ $\mu$ L, some general clinical manifestations such as bacterial pneumonias and sinusitis, occur with increased frequency but with usual clinical presentations and respond well to standard antibiotic regimens. As HIV disease progresses, uncommon presentation of non-HIV associated conditions including tuberculosis, incomplete response to standard courses of antibiotics, more severe and symptomatic clinical course of infections, reactivation of old infections held in check by the immune system like histoplasmosis, tuberculosis, and infection by uncommon pathogens become common.

#### STAGE 4: LATE SYMPTOMATIC AND ADVANCED STAGES OF HIV INFECTION (AIDS)

In the absence of treatment, the HIV infection progresses and the manifestations of late symptomatic disease typically appear when CD4+ counts fall below 200/ $\mu$ L. Opportunistic infections commonly occur. In the absence of prophylaxis, *Pneumocystis jirovecii* pneumonia is the most common and life-threatening infection. Malignancy, HIV dementia and profound constitutional symptoms such as fever, fatigue and weight loss are also hallmarks of late symptomatic disease.<sup>89</sup> Crowe et al. found that the order of appearance of opportunistic infections and malignancies during this stage was strongly correlated with the CD4+ lymphocyte count.<sup>90</sup> Only few opportunistic diseases occur when CD4+ cell counts fall just below 200 cells/ $\mu$ L, although tuberculosis, KS and progressive multifocal leukoencephalopathy are commonly seen. *Cryptosporidium* diarrhea is also a common problem, which is increasingly difficult to treat at this stage. Most of the individuals in the late stage tend to have anemia.

In advanced stage HIV disease, where CD4+ cell counts have fallen below 50/ $\mu$ L, CMV retinitis, *Mycobacterium avium* complex and primary cerebral lymphoma may occur, and HIV-1 associated dementia appears to progress more rapidly. Infections such as *Mycobacterium avium* complex, CMV, *Strongyloides stercoralis*, herpes zoster, or tuberculosis, that normally colonize superficially or are limited to an organ system or a local anatomic region, may invade other tissues or disseminate widely. Simultaneous, clinically significant infection by more than one pathogen is common. The 1987 definition of AIDS was modified in 1992 by the addition of three clinical conditions in the presence of HIV infection: cervical cancer, two episodes of bacterial pneumonia in 12 months, and pulmonary tuberculosis. Increasingly problematic are anorexia, nausea, vomiting, diarrhea, malabsorption, muscle wasting, and weakness.

Death eventually results from extensive disease of the vital organs, most commonly the lungs and presumably from the effects of circulating toxins, electrolyte abnormalities, hematopoietic and circulatory failure and autonomic nervous system damage. Approximately 50% of untreated patients die of infection within one year of the clinical diagnosis of acquired immune-

**Table 66.7:** Survival after Clinical Diagnosis of AIDS, Before Introduction of Effective Antiviral Therapy

Time	Survival (%)
1 yr	50
2 yrs	25
3–4 yrs	5
5 yrs	0

deficiency syndrome, while the chances of survival beyond 5 years have been reported to be nil (Table 66.7). Several of these opportunistic diseases have also been described in HIV-2 infected individuals.<sup>91</sup>

#### Summary

HIV is the causative agent of AIDS. HIV is transmitted primarily through sexual contact and hence genital mucosal surfaces are the portal of entry for HIV virus. HIV is a retrovirus which comprises a nucleoprotein core surrounded by other protein coats. The *pol* gene codes for the viral enzymes reverse transcriptase, integrase, and protease. Although HIV is one of the most recently discovered retrovirus, CD4 was the first retrovirus receptor to be identified. The HIV infection starts with the attachment of HIV through gp120 protein to the CD4 target cell. Virus entry into cells results from the fusion of viral and cell membranes, a process that depends on binding of virus *env* proteins to specific host-cell surface receptors. The HIV replication cycle comprises of two phases. The first phase involves the interaction between viral envelope proteins and specific host cell receptors (CD4 and CCR5/CXCR4) and the second phase involves the synthesis of viral RNA by RNA polymerase II using the integrated provirus as the template, followed by processing of the transcripts of the HIV genomic RNA.

It is well-established now that untreated HIV disease progresses relentlessly in almost all infected persons, from a clinically silent infection to severely damaged immunologic function resulting in the acquired immunodeficiency syndrome (AIDS). Following infection, the time before the onset of clinical disease varies from months to years. Various factors affect the progression of disease include viral and other cofactors, host factors defective co-receptors, SDF-1 gene mutations. There is overwhelming evidence to show that the host builds up immune responses against HIV. However the immune response against HIV is unable to eliminate the virus completely. Genetic traits that may affect progression more importantly include receptor mutations. The disease, if left untreated, leads to death over a median period of about 10 years. However, the time it takes to cover this spectrum varies greatly ranging from one year or less in some patients, to a still unknown upper limit in others. This upper limit has reached nearly 20 years in a few individuals called "long-term non-progressors." Long-term nonprogressors are rare individuals who are infected with HIV, but whose infection does not progress to AIDS. The duration is influenced by many different factors which may be primarily host related like the age and genetic makeup of the individual, but not by gender or mode of acquisition of the virus. Interaction between the host, HIV and environmental factors may determine the course of the disease, clinical manifestations and the rate of disease progression in each individual. Eventually, it causes death in most people. A high percentage of long-term nonprogressors have been shown to have inherited mutations of the CCR5 receptor of T cell lymphocytes. It is believed that the delta 32 variant of CCR5 impairs ability of HIV to infect cells and cause disease.

Various clinical syndromes may occur during the course of HIV disease. The untreated HIV disease can be classified into: Progressive generalized lymphadenopathy, AIDS-related complex, and AIDS, while various stages of disease are: acute seroconversion illness or primary HIV infection, asymptomatic stage of HIV infection, early symptomatic stage of HIV infection and, late symptomatic and advanced stage of HIV infection.

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# 67

## HIV Diagnosis

Jessica Markby • Claire Ryan

### Introduction

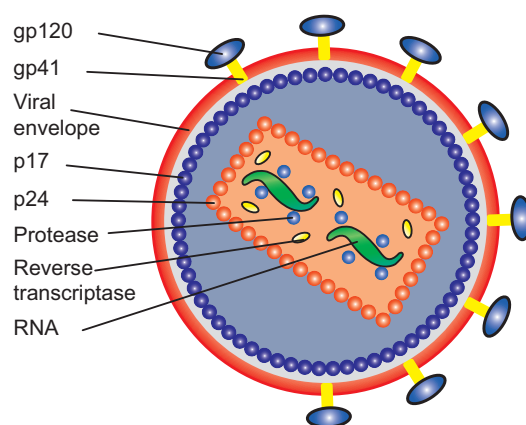
Accurate diagnosis of HIV is crucial to appropriate patient care and management as well as population surveillance and screening programs. In the 1980s, the first available HIV diagnostic methods were all laboratory based, requiring centralized testing, specialized equipment, and a high degree of technical expertise. Currently, as well as improvements in the accuracy of laboratory-based testing algorithms, HIV testing has also evolved to enable point of care (POC) rapid testing. Fourth-generation rapid tests available today provide test accuracies equivalent to laboratory-based assays. This results in faster result turnaround times which enables both decentralization of testing and ensuring that patients actually receive their test results in a timely fashion. This has revolutionized HIV testing programs for developed countries as within specialized clinics results are now available rapidly at the point of testing, enabling appropriate clinical decision making. Similarly, in developing countries, the availability of rapid tests has meant that the logistical problems of specimen transportation and cold chain maintenance for test kits supply can be overcome and that testing can be made available in remote areas that are not serviced by higher tiered health facilities.

This section describes the scientific principles of HIV testing assays; both laboratory-based and rapid tests and describes commonly used HIV testing algorithms and quality assurance of HIV testing.

### Science of Human Immunodeficiency Virus

In order to appreciate the scientific principles of HIV testing methodology, it is first important to understand the basic science of HIV structure. HIV testing strategies target either specific components of the virus (proteins, glycoproteins, or RNA), or the products of the immune response to HIV (immunoglobulins/antibodies).

The HIV virus is simplistic in design comprising very few molecules. As depicted in Figure 67.1, the outer lipid membrane or envelope is embedded with two transmembrane glycoproteins: gp120 and gp41. Within this envelope layer is the nucleocapsid



**Fig. 67.1:** Schematic representation of the structure of HIV (<http://www.avert.org/hiv-virus.htm>).

or viral core, which is comprised of two layers of multimeric proteins; the outer most layer is comprised of the p17 protein and the inner layer of the p24 protein. Within this protein core the viral genomic information is contained as two single strands of RNA along with the viral encoded enzymes *reverse transcriptase* and *integrase*. The invasion and replication stages depicted in Figure 67.2 rely on these viral components.

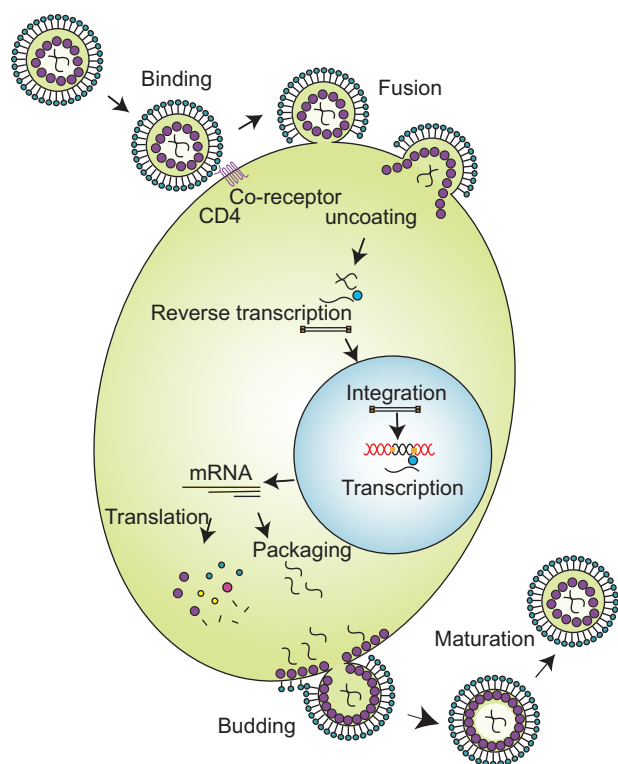
### Stages of HIV Infection and Immune Response

There are typically three phases of HIV infection which are characterized by distinct and measurable profiles of clinical indicators:

- Viremia
- Antibody production, and
- CD4 T lymphocytes levels.

One to 4 weeks after infection with HIV, symptoms of an acute illness develop in about 50–90% of individuals. This is associated with a rapid rise in plasma viremia to often several million copies

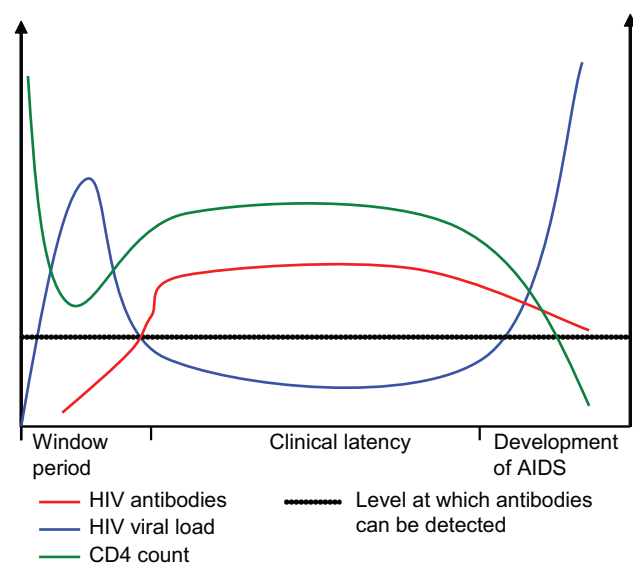




**Fig. 67.2:** Schematic representation of the HIV-1 infectious lifecycle. Binding, fusion, and entry are mediated by the interaction between the viral gp120 and host receptor CD4. The virus is uncoated in the cytoplasm prior to the reverse transcription of viral RNA into DNA. Following integration of the viral DNA into the host cell genome, transcription of the viral DNA occurs, before proteins are translated, processed and packaged into a virion which is able to bud from the cell surface, releasing mature virions. (Used with permission from Kate Jones, Burnet Institute, 2009.)

per mL and a concurrent depletion of CD4<sup>+</sup> T lymphocytes, causing patients to experience “flu-like” symptoms which can include fever, thrush, malaise, myalgia, swollen glands, diarrhea, and rash.

Within 7 days of infection, the adaptive immune response involving B lymphocytes, CD4<sup>+</sup> T lymphocytes, and cytotoxic CD8<sup>+</sup> T lymphocytes begins to mount an anti-HIV immune response. Antibodies to HIV however are not produced until around day 21–28 post infection and seroconversion is subsequently usually complete by 3 to 8 weeks post infection. Immunoglobulin (Ig) M is initially produced followed by IgG and IgA specific to HIV envelope glycoproteins gp41 and gp120, capsid and viral core proteins such as p17 and p24 as well as regulatory proteins. Following this acute phase of infection, there is a marked reduction from peak viremia to a viral load “set point”, usually within 6 to 9 months following infection. There follows a period of clinical latency, often referred to as asymptomatic chronic illness. In most untreated individuals, infection with HIV will ultimately lead to the development of AIDS, which is defined by the acquisition of opportunistic



**Fig. 67.3** The natural progression of HIV infection over time and the relationship between viral load and anti-HIV antibody production.

infections, and occurs due to the decline of CD4 T lymphocytes below a critical level and the significant impairment of cell mediated immunity.

As depicted in Figure 67.3 the viral load peaks during the acute stage of the infection while the antibody titer is low at undetectable levels during this window period of up to 3 months. This period of seroconversion is critical to determining the timing and selection of HIV testing assay given that all rapid tests, enzyme immunoassay (EIA), western blot (WB), and immunofluorescence assay (IFA) rely on the detection of anti-HIV antibodies. Therefore, false negative results are most likely to occur during this window period where patients remain seronegative.

## Principles of HIV Testing

HIV diagnostic tests can be broadly divided into two types: assays that measure anti-HIV antibody production or assays that measure components of the virus such as RNA, proviral DNA or viral proteins (such as p24) or in some cases a combination of the above.

### SEROLOGICAL METHODS

Serological assays for HIV diagnosis rely on the detection of antibodies produced against HIV derived proteins and are thus regarded as an indirect method of testing. Generally, serological assays use whole blood or dried blood spots (DBS) collected by venipuncture or skin prick, or blood fractions (plasma or serum) with variation from assay to assay. Some more recently developed serological assays utilize urine or saliva specimens making specimen collection less invasive.

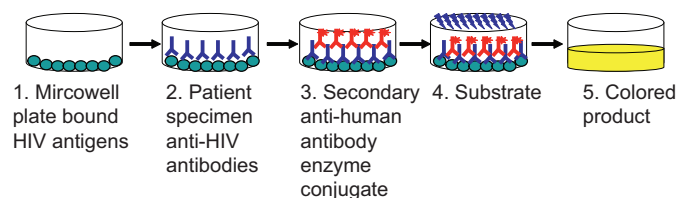
The main problem associated with all serology based HIV assays is the inability to accurately diagnose during the window

period prior to seroconversion. Serological assay results can also be unreliable in advanced HIV infection where immune function is compromised and antibody titers to *pol* and *gag* are decreased and for diagnosis in infancy where maternal IgG (via the placenta) can mask the result.

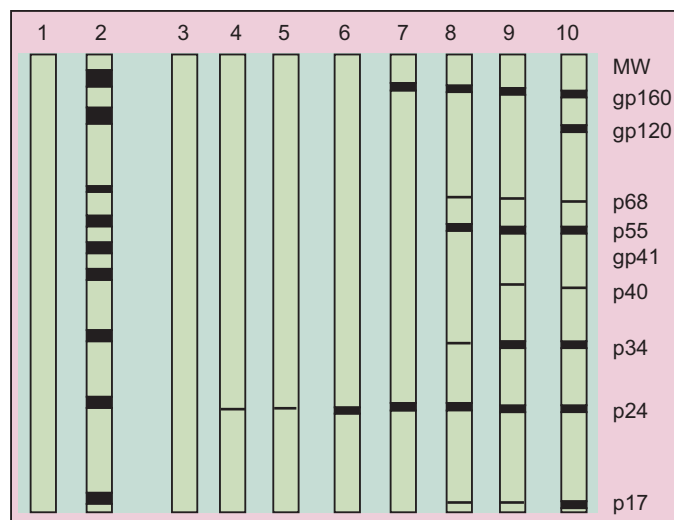
## Laboratory-Based Methods

The first HIV diagnostic assays that were developed for use in laboratories were based on detection of anti-HIV antibodies and remain a mainstay for HIV diagnosis. Laboratory-based HIV tests include the EIA/enzyme-linked immunosorbent assay (ELISA), western blot (WB), and the immunofluorescence assay (IFA). EIA primarily detects IgG and uses indirect, sandwich, or competitive ELISA methodologies. As depicted in Figure 67.4, EIA typically employ kit based recombinant HIV antigens including p24, gp41, or gp120, which are covalently bound to a solid matrix (e.g., microwell plate). Patient serum or plasma is applied to the matrix and if positive, anti-HIV antibodies bind to their cognate well bound antigen. Subsequent addition of enzyme-conjugated anti-human monoclonal antibodies, followed by the enzyme substrate produces a colored product that can be measured colorimetrically. Examples of currently used, FDA approved or CE marked EIA include: Vironostika HIV-1 Plus O Microelisa System (which can also be used for DBS) and the Genetic Systems HIV-1/HIV-2. EIA requires between 60 minutes and several hours to run, as well as cold chain logistics and storage of reagents, specialized equipment and a higher degree of technical proficiency, making them generally unsuitable for smaller laboratories.

Western blot is commonly used to confirm positive EIA results in a traditional laboratory-based algorithm. Similar to EIA, WB detects patient antibodies to HIV using a suspension incubation of patient serum/plasma with a kit based HIV antigen to form an antigen-antibody complex. This complex is then subjected to gel electrophoresis which separates proteins according to size and charge over an electrical gradient. Proteins are then blotted from the gel onto a nitrocellulose membrane before the addition of secondary anti-HIV antibodies conjugated either to alkaline phosphatase or (more traditionally) a radioisotope. Protein bands are then visualized either by using autoradiography or substrate conversion into a colored product to detect HIV protein specific bands (refer to Fig. 67.5 for example). Similar to EIA, WB requires cold chain logistics and storage, expensive and assay specific equipment, and a high degree of technical expertise.



**Fig. 67.4:** Schematic representation of the principle of an EIA.



**Fig. 67.5:** Example of Western Blot band results. Lane 1: Negative control, Lane 2: Positive control, Lanes 3–10: Patient results over time since infection Day 0 to Day 30 ([www.hivinfosource.org](http://www.hivinfosource.org)).

WB has also been shown to produce a relatively high frequency (15–20%) of indeterminate results for negative specimens.<sup>1</sup>

The use of EIA for screening and WB for confirmation of patient samples results in a very high sensitivity 99.3–99.7% and specificity 99.7% if conducted after the window period. Within the window period, however, the sensitivity is significantly reduced.

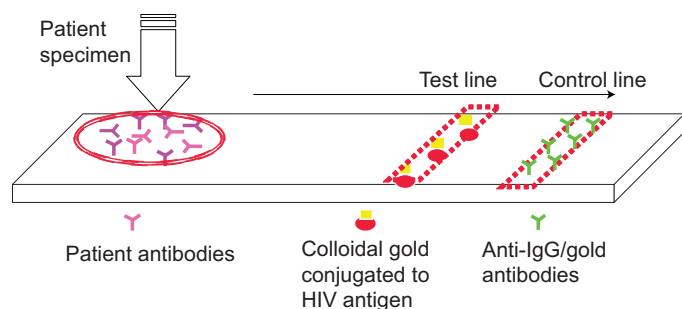
A less common alternative confirmatory or supplementary test to WB is the IFA, which also relies on the detection of patient anti-HIV antibodies. Serum or plasma is incubated with immortalized human T cells that express HIV antigen on their cell membrane in association with MHC molecules. Next, the addition of a secondary antibody (anti-human antibody) that is conjugated to a Fluorescein isothiocyanate (FITC) molecule which emits green fluorescent light (518 nanometers) when excited with an ultraviolet light source (494 nanometers). This is then detected traditionally using microscopy (although it can also be detected and enumerated using flow cytometry). This system is employed in several laboratories in the USA. Specialized, expensive equipment, refrigeration, and a high degree of technical expertise are required for IFA and the process takes more than an hour and a half to complete. It is therefore only suited to low throughput testing facilities. IFA, such as the FDA approved Fluorognost HIV-1 assay, are equivalent in sensitivity and specificity to an EIA or a WB and may also be useful in determining the results from an indeterminate WB.

## Rapid Tests

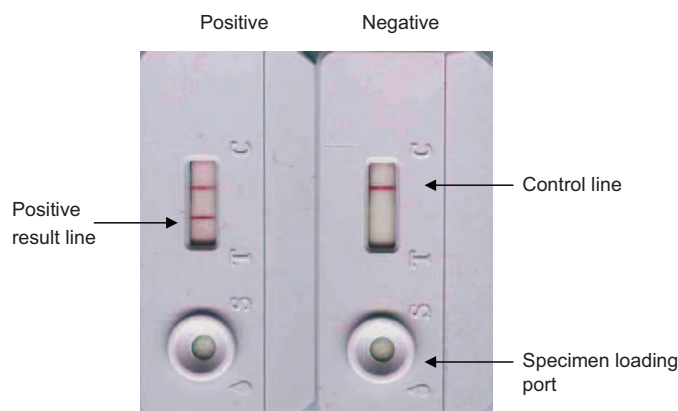
When used in combination as a two or three rapid test algorithm, many currently available, FDA approved rapid test devices have comparable sensitivities, specificities, and predictive values to laboratory-based serological algorithms using EIA and WB. Rapid tests, which often generate results in 10–20 minutes, allow for a

much faster turnaround of results compared to laboratory-based assays and are therefore more suited to point of care testing. As patients do not need to return for results or be followed up by clinic staff, more patients are informed of their result. Several studies have shown that many patients do not return for results and those that know their results are more likely to change risk taking behaviors.<sup>2</sup> In addition, it provides the opportunity for clinicians to make decisions rapidly when an urgent result is required, such as in antenatal clinics, labor wards, and emergency blood product or organ donation. In addition, the ability to make quick decisions about post exposure prophylaxis requirements is possible using rapid test screening of blood products that present a risk of occupational exposure to HIV as well as in sexual assault cases. Rapid tests are generally also more cost effective than laboratory assays averaging around US\$ 2/test (ranging from US\$ 0.50 to 7.5). Additional advantages include the fact that they generally do not require highly trained personnel to complete and interpret the results and in most cases can be transported and stored at ambient temperatures. EIA and WB are not suitable for many small laboratories at provincial or district levels in developing countries where reliable power and water is often not available. Thus in developing countries, the introduction of rapid tests have enabled the decentralization of testing programs, which provide access to testing in even the most remote areas. In some countries, a single rapid test is used to screen patients using a highly sensitive rapid test. Initially reactive patients then require confirmatory testing, which is usually performed by sending a blood sample to a centralized laboratory. Other countries now confirm initially reactive results at the point of testing using a two or three rapid testing algorithm as described below.

There are six types of rapid tests described here defined by their mode of action; the first three of which are most commonly used for testing algorithms. Commonly used examples of each are listed in Table 67.1 illustrating their performance and operational characteristics. The first, most recently developed and most commonly used type of rapid tests, are collectively described as immunochromatographic or lateral flow assays. As depicted schematically in Figure 67.6, patient serum, plasma, or whole blood is applied to the specimen port or pad on the cassette or strip. The specimen then moves by capillary action along the nitrocellulose strip from the loading port to the detection port/window, which holds embedded HIV antigens (depending on



**Fig. 67.6:** Principle of immunochromatographic rapid tests.



**Fig. 67.7:** Example of an immunochromatographic rapid test. Stat-Pak HIV-1/2, illustrating positive (left) and negative (right) results (Adapted from WHO-CDC HIV Assays Operational Characteristics, Report 16 Rapid Assays).

assay these may be gp41 and/or gp120), which in several kits are conjugated to colloidal gold or selenium to facilitate visualization. A control line is also incorporated beyond the test line to ensure that the sample moves all the way through the strip. The control area is usually impregnated with anti-IgG antibodies conjugated to colloidal gold/selenium which bind to patient IgG forming a visual control line. An example of positive and negative results for a lateral flow device (Stat-Pak HIV-1/2) is shown in Figure 67.7.

Immunochromatographic assays are inexpensive (most are under US\$ 2 per test), only require 10–15 minutes for development of results and generally they do not require refrigeration. Most importantly, they are suitable for use in small laboratories or peripheral clinics/VCT sites as they do not require specialized equipment, do not require preparation of patient samples for serum or plasma, nor do they require a high degree of technical expertise to operate or read, and often require only a single step. Given that the results are read visually, there may be some subjective results particularly in the case of weakly reactive positives which may be false positives (higher in low prevalence areas) or early seroconverters. Examples of immunochromatographic rapid tests that are currently available include Determine HIV-1/2, Unigold HIV-1/2, Stat-Pak HIV1/2, OraQUick, HemaStrip HIV-1/2, Colloidal Gold, Sero Strip HIV-1/2.

The second type of rapid test is referred to as a particle agglutination-based test,<sup>3</sup> of which there are two formats. Both rely on the binding of anti-HIV antibodies in patient serum or plasma to HIV antigen covalently linked to latex or gelatin beads. Agglutination or cross-linking of antigen-bead complexes to the antibodies as depicted in Figure 67.8 can then be visualized as small solid particle clumping within a liquid medium. Some devices enhance agglutination by using narrow channels embedded in a clear plastic cassette through which the combined antigen/bead-antibody cocktails move through the cassette by capillary action and after 3–7 minutes, agglutination can be visualized as white clumps (e.g., Capillus HIV-1/2 refer to Fig. 67.8 for





**Fig. 67.8:** Photo of a particle agglutination HIV rapid test. Capillus HIV-1/2—(a) positive result; (b) negative result. Source: WHO-CDC HIV Assays Operational Characteristics, Report 16 Rapid Assays.

photograph of positive and negative results). Other particle agglutination rapid tests use microwell plate-based agglutination with antigen coated gelatin particles (e.g., Serodia HIV-1/2, MicroRED HIV-1/2). The latter are the least rapid and most technically demanding of all rapid tests and are only suitable for use by trained laboratory personnel. In addition, agglutination assay kits require refrigeration and cold chain logistics for reagents and difficulty has been reported widely for agglutination assays in determining whether weak agglutination reactions are positive or negative. Operator variability can be an issue.<sup>3</sup>

A third type of rapid test is known as membrane immunoconcentration devices and is also referred to as flow through assays. The patient specimen (plasma or serum although some can use whole blood) flows through solid phase capture technology using a porous membrane which contains immobilized HIV antigens conjugated to colloidal gold or selenium. The specimen is absorbed onto the membrane and the binding of anti-HIV antibodies to the antigen conjugate can be visualized as a line or dot in the membrane where immunobinding is focused. Several steps are often involved including specimen loading as well as conjugate and flow buffer addition. The whole assay takes between 5–15 minutes depending on the kit. Most kits require refrigeration, some differentiate between HIV-1 and 2 and most are more expensive than most immunochromatographic assays ranging from US\$ 4 to US\$ 8 per test.

A fourth and less commonly used HIV rapid test is the Immunodot EIA which incorporates solid phase HIV antigens fixed to teeth-like projections. In one example a mixture of three synthetic HIV antigens are used (two epitopes of gp41 and one gp120). The teeth are incubated in chamber wells containing diluted patient serum whereby anti-HIV antibodies are captured at the antigen containing binding site (clustered as a dot). Subsequent incubations that follow the sequence of a conventional EIA are then carried out as the card is moved between chambers containing secondary antibodies, conjugates and substrates. Upon completion, the teeth develop focused visual dots (usually purple) including control dots. Dots indicate HIV-1 and HIV-2 infection separately.

A fifth type of HIV rapid test is referred to as a red cell or hemagglutination assay and utilizes kit based HIV antigen complex to red blood cell protein antibody complexes. When added to the patient whole blood, the patients HIV antibodies cause agglutination of the patients red blood cells in less than 5 minutes if HIV positive.

A sixth type of HIV semi-rapid test category is the magnetic bead assays. An example of a magnetic bead assay is the Bionor HIV-1/2 which enables distinction of HIV-1 and HIV-2 and employs an ELISA-based methodology with magnetic beads as the solid matrix to which HIV antigens (gp41, gp120, gp36, and p24) are conjugated. The beads and bound patient antibodies are then separated using a magnet and subsequently ELISA-based colorimetric detection is carried out.<sup>4</sup>

## VIRUS PARTICLE DETECTION

The second major group of HIV diagnostic assays involves the *direct* detection of HIV particles either at the protein or the nucleic acid level. Direct HIV diagnostic assays include p24 antigen detection assays, nucleic acid-based assays, and cell culture assays. Direct detection methods allow earlier detection compared to serological methods as they do not rely on seroconversion for an accurate result. They therefore can be used during the window period with high sensitivities, often within 10 days of infection. They are also effective in testing immunocompromised AIDS patients and for early infant diagnosis. Unfortunately, most direct HIV diagnostic assays require a high degree of technical expertise to perform and are not suitable for small laboratories or lower tiered facilities. Specialized equipment is required for the assays and the tests are significantly more expensive than most serological assays. However, direct assays are widely used in centralized laboratories particularly in developed countries for confirmation of initially positive serology results as well as for early detection in adults and infants in both developed and developing settings.

### p24 Antigen Detection

The concentration of free HIV capsid antigen p24 in the blood increases to detectable levels between 1 and 3 weeks after HIV infection. Therefore, the p24 assay is suitable to use in individuals with recent exposure to HIV that may remain seronegative. Some p24 assays employ a sandwich ELISA-based assay to capture the p24 antigen in patient serum using kit based, plate bound, anti-p24 antibodies followed by subsequent addition of a secondary anti-p24 polyclonal antibody which is biotinylated enzyme (horseradish-peroxidase) conjugated to streptavidin, followed by substrate addition, thus enabling colorimetric detection and quantification.

Standard p24 ELISA assays have a sensitivity ranging from 10–60% depending on the assay with a lower limit of detection at 10 pg/ml. Thus in up to 60% of patients, p24 may not be detected. This is, in part, due to anti-p24 antibody production in patients which block binding sites on p24 resulting in the free p24 levels possibly being below assay detection levels. Modifications to this basic assay have been made to enhance its sensitivity thereby ensuring that the assay is suitable for diagnosis of seronegative patients as well as early infant diagnosis. These modifications include the addition of a heat denaturation step which releases p24 that is bound to anti-p24 antibodies in the patient blood

**Table 67.1:** Test Kit Characteristics

1. Rapid Test Kits						
Kit name	Type	Sensitivity	Specificity	Cost US\$	Reference	Manufacturer
HIV-1/2 Stat-Pak	ICA	98.8–100	98.1–99.9	1.10–1.35	WHO, 16	ChemBio Diagnostics
Retrocheck HIV/CORE HIV-1&2	ICA	98.8–100	97.8–99.8	0.7–0.85	WHO, 16	QualPro Diagnostics
DoubleCheck Gold HIV-1&2	ICA	98.8–100	99.3	1.20–1.32	WHO, 14	Orgenics Ltd
Determine HIV-1/2	ICA	99.6	99.9	1.00–1.20	Mayhood, 2008	Abbott
Uni-gold HIV Recombigen HIV Test	ICA	99.5–100	99–100	2.94	Greenwald, 2006	Trinity Biotech
OraQuick HIV-1/2 Rapid HIV-1/2	ICA	98.4–99.7	99.6–99.9	3.15	Greenwald, 2006	OraSure Technologies
HemaStrip HIV-1/2	ICM	94.5–99.6	98.8–100	1.85–2.5	WHO, 14	ChemBio Diagnostics
Serodia HIV-1/2	PA	98.5–100	98.5–100	2.8	WHO, 16	Fujirebio
Capillus HIV-1/2	PA	99.7	99.8	1	Mayhood, 2008	Trinity Biotech
Genie II HIV-1/HIV-2	IC	97.7–100	98.1–100	2.55	WHO, 14	Bio-Rad
HIV TRI-DOT	IC	98.9–100	99.1–100	2	WHO, 11	J. Mitra and Co. Ltd.
MedMira HIV-1/2	IC	95.5–100	94.1–99.6	3	WHO, 12	MedMira Laboratories
InstantCHEK-HIV-1 + 2	ICM	96.5–100	95.2–99	1	WHO, 14	EY Laboratories, Inc.
HIV-1/2 DoubleCheck	ID	99.6–100	98.6–100	2	WHO, 11	Orgenics Ltd
Span Comb AIDS Visual	ID	99.6–100	84.5–91.5	0.5	WHO, 11	Span Diagnostics Ltd.
Immunocomb II BiSpot HIV-1 & 2	ID	99.6–100	97.6–100	1.7	WHO, 16	PBS Orgenics
Bionor HIV-1 & 2	MB	99.6–100	97.6–100	2.5	WHO, 11	Bionor A/S
SD Biotline HIV-1/2 3.0	ICM	97.7–100	97.6–99.9	1.1	WHO, 14	Standard Diagnostics
Efoora HIV Rapid	ICM	91.9–98.6	95.6–99.3	0.75–2.6	WHO, 14	Efoora Inc.
GENEDIA HIV-1/2 Rapid	ICM	97.7–100	98.1–100	0.93–1.0	WHO, 14	Green Cross Life Science Corp.
Advanced Quality HIV Rapid Test	ICM	98.2–99.8	98.8–100	0.8–0.9	WHO, 16	InTec Products
First Response HIV-1/HIV-2 WB	ICM	95.5–100	95.8–100	1.15	WHO, 12	PMC Medical Pty.
2. ELISA and Western Blot						
Kit name	Type	Sensitivity	Specificity	Cost US\$	Reference	Manufacturer
Vironostika Uniform II Plus O Microelisa system	EIA	99.6–100	99.7–100	1.5	WHO, 11	Biomerieux
Detect-HIV	EIA	98.6–100	94.0–99.2	2.5	WHO, 16	Adalitis
HIV EIA	EIA	99.6–100	98.6–100	0.6	WHO, 10	Anilabsystems
Enzygnost Anti-HIV-1/2 Plus	EIA	99.6–100	99.1–100	1	WHO, 11	Dade Behring
Abbott Recombinant HIV-1/HIV-2	EIA	98.5–100	98.5–100	1.7	WHO, 16	Abbott
UBI HIV 1/2/EIA	EIA	99.6–100	99.7–100	1	WHO, 16	United Biomedical Inc.
Imx HIV-1/HIV-2 3rd generation Plus	EIA	98.9–100	96.4–99.4	3.0–4.0	WHO, 16	Abbott GmbH Diagnostika
New Lav-Blot-I	WB	98.1–100	96.8–100	11.6	WHO, 16	Sanofi Diagnostics Pasteur
HIV-1 Western Blot Kit	WB	98.5–100	98.7–100	17.7	WHO, 16	Bio Genex
Pepti-Lav 1-2	WB	96.4–99.9	98.1–100	21.5	WHO, 16	Sanofi Diagnostics Pasteur
IFA anti-HIV-1	IFA	96.9–99.8	98.3–100	5.6	WHO, 16	Waldheim Pharmazeutika
IFA anti-HIV-2	IFA	93.1–99.7	98.2–100	6	WHO, 16	Waldheim Pharmazeutika
3. Combination HIV Antigen/Antibody Assays						
Kit name	Type	Sensitivity	Specificity	Cost US\$	Reference	Manufacturer
Enzygnost HIV Integral II	EIA	97.7–100	98.7–100	NA	WHO, 15	Dade Behring
Genedia HIV AG-Ab ELISA	EIA	97.7–100	98.1–100	0.4–0.45	WHO, 15	Green Cross
Murex HIV Ag/Ab Combination	EIA	97.7–100	97.6–99.9	0.8–1.2	WHO, 15	Abbott Diagnostics
Vironostika HIV Uniform II Ag/Ab	EIA	97.7–100	97.1–99.8	1.48–1.95	WHO, 15	Biomerieux

ICM, immunochromatography; PA, particle agglutination; IC, immunoconcentration; ID, immunodot; HA, hemagglutination; MB, magnetic bead; EIA, enzyme immuno-assay; WB, Western blot.

and a signal amplification step using the addition of a biotinyl tyramide reagent to increase the lower limit of detection (ELAST ELISA Amplification System). A further modification involves the simultaneous detection of HIV antibodies together with detection of p24 antigen. Dual assays are also referred to as fourth-generation assays and increase the sensitivity at earlier time points in the window period thus enabling detection reportedly 7 days earlier than standard serological assays.<sup>5</sup> They are therefore recommended in the United Kingdom as screening assays.<sup>6</sup>

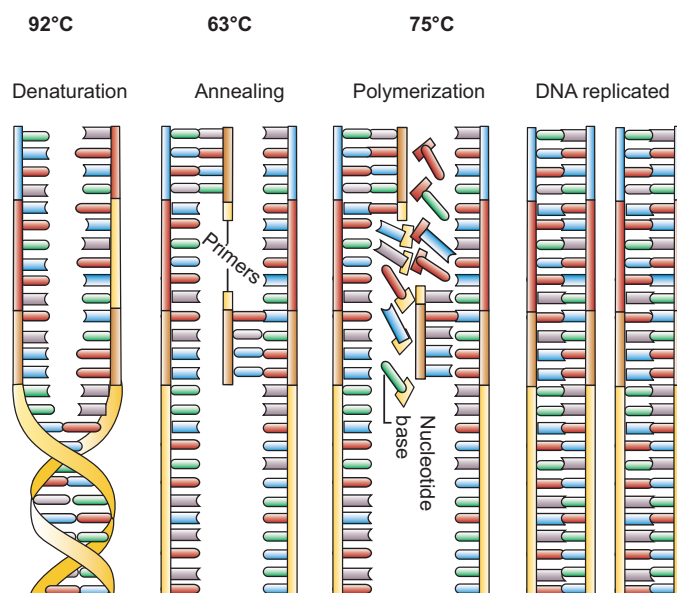
Most p24 assays are significantly less expensive than nucleic acid-based assays for HIV diagnosis. Additionally, they are generally simpler to perform and present a much lower risk of cross contamination and false positive results. Recently, a new rapid test for the detection of p24 has been developed with an incorporated magnetic immunochromatography/flow through device. Validation of this device by the Centers for Disease Control and Prevention (CDC) indicates promising performance results at lower costs to alternative p24 assays.<sup>7</sup>

## Nucleic Acid-Based Assays

Direct detection of HIV at early stages of infection is most commonly achieved using molecular assays that detect HIV nucleic acids. Nucleic acid-based assays detect specific HIV genes including the most conserved *gag* and *pol* sequences that are generally not the target of mutations. Molecular diagnosis of HIV can be performed both qualitatively and quantitatively and the use of these two methodologies is often interchangeable. Molecular diagnosis has generally been reserved for resource rich countries where qualitative or quantitative assays are commonly used for early detection of infection in adults (during the serological window period), routine infant diagnosis, in some laboratory algorithms as a supplementary or alternative assay to WB for confirmation of adult diagnosis as well as for routine use of quantitative assays for monitoring HIV patients for treatment candidacy and treatment efficacy. Due to the fact that these assays require specialized laboratory settings with expensive equipment, highly trained technicians, a high degree of quality assurance, and reagent costs are significantly higher than for serological methods; their use in resource-constrained settings has been limited. However, over the last 5 years an increasing number of developing countries have adopted molecular diagnostic assays where less expensive, non-molecular methods are not accurate such as for early infant diagnosis programs and in fewer cases for quantitative HIV patient treatment monitoring. In particular many developing countries in Africa, Latin America, and the Asia-Pacific region now routinely use molecular-based assays for diagnosis of HIV in early infancy.

### Qualitative Molecular Assays

The determination of HIV diagnosis using a qualitative molecular assay can be achieved using DNA or RNA-based methods. In the former, proviral HIV DNA typically within the *gag* or *pol* genes is amplified using a polymerase chain reaction (PCR). As depicted in Figure 67.9, extracted patient DNA/RNA is



**Fig. 67.9:** Three stages of a polymerase chain reaction. Denaturation, annealing and polymerization and typical temperatures used for cycling.

added to a master PCR mix containing deoxyribonucleotide triphosphates (dNTPs, monomeric nucleic acid bases), DNA polymerase (Taq), primers,  $MgCl_2$  and if appropriate reverse transcriptase (RT) enzyme for a RT-PCR. The PCR mix is then placed in a PCR machine which cycles between three key temperatures which correspond to DNA denaturation (unzipping of double stranded DNA), primer annealing (a short sequence of DNA complementary to single stranded target DNA binds), and polymerization (the addition of complementary dNTPs bind along the strand catalyzed by the polymerase). The result after one such cycle is the production of an identical copy of the target DNA. This process is repeated up to 30 times with a doubling or exponential increase in the amount of DNA with each cycle such that after 30 cycles the number of double stranded DNA molecules would be 1,073,741,824.

Amplified DNA product/amplicons can be detected using a variety of methods including detection of the amplified product by gel electrophoresis, real time fluorescence, or enzymatic/colorimetric visualization. Enzymatic/colorimetric detection is performed by hybridizing denatured, amplified DNA to microplate bound biotinylated probes followed by the addition of avidin-conjugated enzyme such as horseradish peroxidase, substrate is then added which results in a colored product that can be visualized and subjected to colorimetric analysis which may be qualitative or quantitative depending on the assay. Other qualitative PCR assays can also be used to detect different HIV subtypes and drug resistance mutations.

### Quantitative Molecular Assays

Quantitative assays also referred to as viral load assays are used in many developed settings for HIV diagnosis confirmation but their



capabilities make them specifically suitable for quantifying HIV for the purposes of monitoring HIV patients for viral progression. As with qualitative PCR, viral load can be used for HIV diagnosis as a confirmatory assay for patients that test positive with an HIV screening assay and are often used as a supplementary or confirmatory assay in place of WB or IFA. Viral load assays can be used for early diagnosis of adult infection during the window period and for early infant diagnosis as a substitute for conventional qualitative PCR. Viral load however is regarded as the standard of care for monitoring HIV patients in developed countries, but remains relatively rare in developing countries. Its use however, is expanding, particularly with the growing body of evidence for inaccuracies in immunological-based monitoring<sup>8,9</sup> as well as the cost ineffectiveness of not using viral load monitoring on public health expenditures is made more evident.<sup>10</sup>

The quantity of virus is expressed as copies of virus (usually RNA) per mL of plasma or alternatively as international units (IU) per mL. Variability of viral load readings is common from day to day for one patient and from assay to assay hence the importance of looking at trends and multiple readings. The main methods used for viral load assays for which FDA approved diagnostic kits are available are reverse transcription (RT) PCR previously described (e.g., Amplicor [Roche]), branched DNA PCR (e.g., Versant [Bayer]) which does not involve amplification but rather a series of hybridization and probe based capture of target sequences and subsequent enzymatic visualization<sup>11</sup> and nucleic acid sequence-based amplification (NASBA, e.g., Nuclisens [BioMérieux] which amplifies RNA using a PCR at a single temperature using multiple primers and enzymes, making it more rapid reviewed in).<sup>12</sup> Each type of assay requires assay specific equipment including in some cases automated robots components (e.g., Roche Ampliprep).

The development of fluorescence-based detection assays, in particular real time PCR which utilizes fluorescent dyes such as SYBR green and Taqman probes enables highly accurate quantification of double stranded DNA products in a PCR. Typically in a real time PCR assay, fluorescence resonance energy transfer (FRET) is employed whereby two fluorescent dyes one of high energy (reporter) and one of low energy (quencher) are conjugated to the 5' end and 3' end of the probe. The energy is transferred from high to low (reporter to quencher) emitting a low energy when the two dyes are in close proximity to one another and the probe is intact. However, as DNA polymerization occurs, the probe which is designed to sit between the forward and reverse primers is cleaved by the DNA polymerase enzyme when it encounters the probe at the end of polymerization. This cleavage of the probe causes separation of the reporter and quencher, which alters the energy and wavelength of light emitted. The higher energy now being emitted from the reporter can be detected and recorded with each PCR cycle enabling real time quantification of PCR products by way of fluorescent enumeration. Real time PCR is less susceptible to cross contamination due to a closed tube system, however it requires specialized equipment and relatively expensive reagents. It is used in developed countries for early HIV diagnosis

or confirmation as well as viral load monitoring in developed and more recently in some developing countries as an alternative to conventional quantitative PCR techniques described previously.

### ***Pediatric Diagnosis using Nucleic Acid Testing***

Antibody tests commonly used for adult HIV diagnosis are not reliable for diagnosis of HIV exposed infants under 18 months due to the fact that maternal HIV antibodies may still be present in the child, (maternal anti-HIV IgG crosses the placenta), creating the need for additional methods of testing. Without anti-retroviral therapy (ART), 20–45% of HIV-infected women transmit the virus to their infants. There is a high risk of death before 2 years of age among HIV-infected infants. Given the increased availability of ART in resource-constrained settings, the World Health Organization (WHO) recommends that early infant virological testing (EID) be carried out in order to allow initiation of ART for HIV-positive infants.<sup>13</sup> EID enables identification of HIV-positive infants in order to provide appropriate and early treatment and care, reducing infant morbidity and mortality. In addition, in the case of HIV-negative infants, EID also enables for early decisions around prevention, including alternative infant feeding options.

Although several DNA and RNA-based assays can be used for infant diagnosis, the most widely used and validated method, which is endorsed by the CDC and WHO as the most suitable assay for the early diagnosis of HIV in infants and FDA approved by the US, is a qualitative HIV DNA PCR (Roche Amplicor version 1.5) assay using whole peripheral blood.<sup>14</sup> Proviral HIV DNA is isolated from the nucleus of peripheral blood leukocytes. More recently, this assay has been adapted for use with whole DBS, making it more suitable for countries with constrained cold chain logistics networks.<sup>15,16</sup> Molecular diagnosis of infants in the first month of life shows a very high sensitivity and specificity using the gold standard Roche Amplicor 1.5 reaching 98% and 100%, respectively<sup>17</sup> and reaching 100% at 2 months of age.<sup>18</sup> The Roche Amplicor HIV DNA PCR is relatively expensive at approximately US\$ 24 per test and requires a high degree of technical expertise, time (each run requires about 6 hours), specialized equipment, and quality control.

### **Cell Culture**

Diagnosis of HIV using cell culture is not commonly used, especially in light of the ease of use, speed, and accuracy of results obtained from serological and direct virus detection assays described previously. However, virus isolation can be achieved by co-culturing patients' peripheral mononuclear cells with healthy donor leukocytes or T-cell lines (indicator cells). HIV in patient mononuclear cells can be detected by changes in the indicator cells in culture; however due to the long time required to culture cells (greater than 2 weeks), it is generally not used for diagnosis of HIV infection but rather than for characterization of the virus including analyses of drug resistance profiles using for example quantitative plaque reduction assays.

## Impact of Genetic Diversity on HIV Testing

There are two distinct types of HIV—HIV type 1 (HIV-1) and HIV type 2 (HIV-2). HIV-1 is the most widespread, and is responsible for the majority of infections worldwide. HIV-2 infections are generally restricted to certain geographical areas, namely Western Africa and Western India. HIV-1 can be further divided into three main groups termed group M (main), group O (outlier), and group N (non-M and Non-O). Group M viruses are the most widespread, and in turn are divided into nine different subtypes (A, B, C, D, F, G, H, J, K) and a number of different recombinant forms which result from the recombination of two or more subtypes. As serological tests target antibodies specific to HIV, or HIV antigen, they are far less subject to the genetic diversity displayed by HIV than nucleic acid-based tests, which target specific sequences within a reasonably conserved HIV gene.

As nucleic acid-based tests are predominantly used for confirmation purposes, or for early infant diagnosis, the clinical indications of HIV must be taken into consideration in a diagnosis. The majority of the issues that arise as a result of HIV genetic diversity concern HIV monitoring, in particular, HIV viral load testing.

## HIV Testing Algorithms

An algorithm refers to the combination and specific sequence of assays used in a testing strategy. In HIV diagnosis there are many variations of testing algorithms used in different countries and also within countries depending on the setting and use. For example, different testing algorithms may be used for blood screening for transfusion, HIV screening at Voluntary Counseling and Testing (VCT) sites, antenatal clinics, and for HIV surveillance/research. The positive predictive value (PPV) (or likelihood of a positive test result being correct using a single test) is dependent on the HIV prevalence. With a decrease in HIV prevalence, PPV also decreases (e.g., HIV prevalence of 10% confers a PPV of 97%, but at a prevalence of 2% the PPV is 87% using Uni-Gold rapid test).<sup>19</sup> Sequential testing using two or three rapid tests in series or parallel, however, has been shown to be significantly more sensitive and specific with higher positive and negative predictive values (approaching 100% depending on the assays used). As previously mentioned, some testing algorithms involve laboratory-based testing, others employ rapid testing which can be carried out at the point of care/testing, and others involve both point of care screening and laboratory-based assay confirmation. Testing algorithms may be done in parallel where all tests in the algorithm are carried out simultaneously or by serial testing where the first test is used as a screening test and if it is positive then subsequent confirmatory/supplementary tests are used. In resource constrained settings, serial testing is common as it offers a more cost effective approach. Some of the key factors considered when testing algorithms are developed include individual test performance indicator data (specificity, sensitivity, and positive and negative predictive values specific to each setting dependent of HIV prevalence), as well as indicators for tests when used in combination and sequence in an algorithm, test availability within countries including approval labeling, ease of

use, cost, storage conditions for test reagents, equipment required, training of personnel required, specimen type, and the potential to differentiate between HIV-1 and HIV-2.

Tests in an algorithm should not share the same false positives and negatives. Generally speaking, an HIV-positive diagnosis is dependent on the concurrence of at least two positive assay results. When the results from these two tests do not agree the result is referred to as discordant, indeterminate or inconclusive. In such cases, a third assay may be employed as a “tie-breaker”, or alternatively, the patient may be requested to return again after 2 or more weeks (or after the window period) for follow-up testing. Indeterminate results may be caused by the patient being in the window period and exhibiting seronegativity for less sensitive assays. Alternatively, indeterminate results may be caused by assay inaccuracies including false positives or negatives.

Historically, a single EIA was first used in 1985 for screening donated blood. Following this, VCT centers were established and blood was sent to laboratories for testing using EIA. The occurrence of false positives (particularly in low prevalence areas) led to the need to develop a two-test algorithm by the CDC in 1989. The first use of a two test algorithm was the laboratory-based EIA followed by either a WB or IFA. This became the gold standard globally. Patients typically waited 1–2 weeks for results in developed countries and much longer in developing countries. This greatly reduces the number of patients who learned their results due to patients being lost to follow-up. Even moderate waiting times (107 minutes) for results can lead to up to 55% of patients not waiting to receive their results compared to shorter times resulting in significantly more patients receiving their results.<sup>20</sup>

Currently there are many algorithms in use globally, however in 2009 the CDC issued a report on HIV testing algorithms which outlines several specific testing algorithms for point of contact (POC) testing and laboratory testing.<sup>19</sup> The report outlines four POC algorithms which use assays that are simple and rapid without blood preparation and that can enable results reporting at the same visit. The first algorithm, developed in 2004, is designed to screen out negative patients at the POC and refer initially positive specimens for laboratory confirmation. It is a combined POC screening using a single rapid test on blood; and for reactive specimens distinct confirmatory assay(s) are carried out. The second POC algorithm employs two different sequential rapid tests on blood. The third POC algorithm is a variation on algorithm 2, as it involves screening using oral specimen with one assay, followed by confirmation for initially reactive specimens using blood with a second assay. The fourth POC algorithm involves three different rapid tests performed sequentially and is suited to low resources settings where higher tiered laboratories are not available/accessible. The third test is employed as a “tie-breaker” if the results from the first two tests do not agree. Laboratory-based algorithms involve assays that include a combination of rapid tests or more complex assays that require blood preparation. They are used for a variety of purposes depending on the setting and use and include screening as well as confirmatory testing of POC reactive specimens.

## Quality Assurance

Quality assurance (QA) is a vital component of HIV diagnosis whether using POC and/or laboratory-based algorithms. It is essential to ensure that the HIV testing process has been carried out properly and that the kit reagents are performing as intended. Although FDA approved and validated assays provide highly reliable results, there is always potential for human error in testing and recording of test results. A comprehensive QA program for HIV testing is therefore vital to provide identification of potential mistakes and to reduce or prevent ongoing errors. Essential components of a comprehensive QA program for HIV testing include appropriate training, supervision, and assessment of testing personnel as well as provisions of written instructions typically in the form of standard operating procedures are crucial preparatory measures for quality assured HIV testing. In addition, the provision of appropriate test kits, reagents and consumables that are standardized, approved and validated need to be used and controlled for stock management. An appropriate and safe environment for testing must also be provided. Documentation of testing activities is also an important component of quality control in order to trace potential sources of error or confusion. During the testing practice there are several practical measures of quality control that should be employed as part of quality assured HIV testing including internal and external controls. External quality assessment schemes (EQAS) are also an important component of QA for HIV testing and should be carried out on a regular basis using an established program.<sup>19</sup>

### Summary

In this chapter, we have illustrated the key principles of HIV diagnosis as well as the practical aspects of achieving accurate results in clinical practice. Understanding the structural and functional molecular components of HIV as well as the kinetics of the immune response to HIV infection is critical to understanding how diagnostic assays are designed to work. Indirect diagnostic assays or serological assays rely on the detection of anti-HIV antibodies and have been designed for use both in the laboratory and more recently in clinical or field-based diagnostic settings. There are many different serological HIV diagnostic assay formats that rely on different test principles including Western blotting, immunochromatography/concentration, immunoprecipitation, particle agglutination, and immunofluorescence. Direct diagnostic assays, however, detect the presence of HIV viral particles either at the protein (e.g., p24) or nucleic acid level (RNA or DNA). Accurate early pediatric diagnosis requires direct viral particle detection due to the fact that maternal anti-HIV antibodies may be present in the circulation of the infant even if the HIV virus has not been transmitted. In practice, a clinical/laboratory testing algorithm is required that employs more than one assay. This involves the combination of two or more tests that use different testing principles (e.g., EIA and Western blot), and which offer an increased, combined sensitivity and specificity. A myriad of different testing algorithms are used globally with various combinations of assays, which differ in different settings/purposes such as blood donor screening, labor wards or voluntary counselling and testing. Regardless of the algorithm used, robust quality assurance of HIV testing is an integral component of ensuring accurate results are provided to the patients to determine appropriate HIV interventions and care.

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# 68

## Pharmacology of Antiretroviral Drugs

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### Introduction

The introduction of the first antiretroviral agent, zidovudine, in March 1987 heralded a new era for those who were suffering from HIV infection. The early 1990s saw monotherapy as the standard of care but initial hopes of effective HIV management were short-lived as patients experienced treatment failure.<sup>1</sup> In 1995, the results of the European-Australian DELTA Study and the American ACTG 175 Study demonstrated the superior efficacy of dual NRTI therapy over monotherapy in reducing AIDS defining illnesses and death.<sup>2-4</sup> The introduction of HIV RNA quantification techniques offered an objective measure of antiviral efficacy and opened broader insights into relationships between pharmacokinetic and pharmacodynamic properties of antiretroviral drugs and their efficacy. In 1997, protease inhibitors were developed following elucidation of the molecular structure of HIV protease and their use in combination with other antiretroviral agents gave rise to the term Highly Active Antiretroviral Therapy (HAART).<sup>5,6</sup> Since then, numerous additional antiretroviral agents and at least three new classes of antiretroviral drugs have been added to the list of agents available for the management of HIV (Fig. 68.1, Table 68.1). In areas with access to the therapy, HIV is now considered as treatable chronic illness with viral suppression achievable even in heavily pretreated patients.

The availability of such a variety of agents that can be used in multiple different combinations gives rise to many potential pharmacokinetic (PK) and pharmacodynamic (PD) interactions. Hence, it is necessary to understand the mechanisms of action as well as the PK and PD characteristics of commonly used antiretroviral agents to gain maximum durable benefit and make appropriate drug choices for patients. This chapter provides a basic overview of the pharmacokinetic and pharmacodynamic principles relevant to the antiretroviral medications and summarizes the currently available antiretroviral agents, including their mechanisms of action, basic pharmacology, toxicities, and important drug interactions. The role of Therapeutic Drug Monitoring (TDM) in clinical practice and potential new agents

in development is also discussed. As this chapter cannot cover all aspects of pharmacology in a therapeutic field that develops as rapidly as HIV, internet references for information sources on drug prescribing and interactions are provided at the end of the chapter.

### Life Cycle of HIV

The HIV life cycle, understanding of which has been pivotal to the development of the 6 currently used antiretroviral drug classes,

1987	Zidovudine (AZT)
1991	Didanosine (ddI)
1992	Zalcitabine (ddC)
1994	Stavudine (d4T)
1995	Lamivudine (3TC), Saquinavir (SQV)
1996	Ritonavir (RIT), Indinavir (IDV), Nevirapine (NVP)
1997	Nelfinavir (NFV), Delavirdine (DLV), 3TC/ZDV (Combivir - CBV)
1998	Efavirenz (EFV), Abacavir (ABC)
1999	Amprenavir (APV)
2000	Lopinavir/ritonavir (kaletra), Trizivir (ZDV/3TC/ABC)
2001	Tenofovir (TDF)
2002	
2003	Enfuvirtide (ENF), Atazanavir (ATV), Emtricitabine (FTC), Fosamprenavir
2004	ABC/3TC (Kivexa), TDF/FTC (Truvada)
2005	
2006	Darunavir (DRV), TDF/FTC/EFV (Atripla)
2007	Raltegravir (RAL), Maraviroc (MVC)
2008	Etravirine (ETR)

**Fig. 68.1:** Timelines for licensing of antiretroviral agents for treatment of HIV-1 infection. Figure describes the year of licensing of each antiretroviral with the generic drug name followed by commonly used mnemonic in parentheses.

**Table 68.1:** Currently Available Antiretroviral Medications and Drug Classes

NRTI	NNRTI	Protease inhibitors	Integrase inhibitors	Maturation inhibitors	Fusion inhibitors
Zidovudine	Nevirapine	Saquinavir	Raltegravir	Maraviroc	Enfuvirtide
Didanosine	Delavirdine*	Ritonavir			
Stavudine**	Efavirenz	Indinavir			
Lamivudine	Etravirine	Nelfinavir			
Abacavir		Lopinavir/ritonavir			
Tenofovir		Atazanavir			
Emtricitabine		Fosamprenavir			
Zalcitabine* (discontinued)		Tipranavir			
		Darunavir			

\*Discontinued.

\*\*Discontinuation recommended by WHO.

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

can be broadly classified into 11 different stages, 5 of which are targets for antiretroviral agents.

**Attachment:** Interactions between the viral envelope protein gp120 and the CD4 receptor, expressed on T-cells, macrophages, monocytes and dendritic cells, cause a conformational change in the host cell membrane exposing the beta-chemokine receptors CXCR4 or CCR5. The third variable (V3) loop of gp120 binds to these chemokine receptors, with differences in V3 loop determining the affinity of circulating virus for either the CCR5 or CXCR4 receptors—termed CCR5 or CXCR4 tropism. Determination of tropism classifies an individual's virus as being CCR5-tropic, CXCR4 tropic or mixed tropic, depending on the relative affinity of the virus for these receptors in cell-based infectivity assays or based on genotype sequences of the V3 loop sequence of gp120 that can predict viral tropism. Binding to both the CD4 receptor and these chemokine co-receptors results in change in the virion structure to allow direct contact between the viral envelope and the host cell membrane. Maraviroc, a CCR5 antagonist, binds to cellular CCR5 co-receptors and prevents attachment of CCR5-tropic virus and is used as an antiretroviral agent in patients with CCR5-tropic virus.<sup>7</sup>

**Fusion:** Another viral envelope protein, GP41, facilitates fusion between the viral envelope and cell membrane through interactions between two repeat sequences in the gp41 peptide known as heptad 1 and heptad 2. This interaction leads to collapse of the extracellular portion of gp41 envelope allowing fusion. Enfuvirtide, a fusion inhibitor, is a synthetic peptide derived from the heptad 2 sequence, which competitively binds to heptad 1, prevents change in gp41 and therefore inhibits fusion.<sup>8</sup>

**Reverse Transcription:** Fusion between the viral and host cell membranes allows delivery of the viral core into the host cell cytoplasm. Shedding of the viral capsule P24 protein exposes single-stranded viral RNA, which is transcribed to single-stranded complementary DNA (cDNA) by HIV reverse transcriptase. After DNA-dependent polymerase creates double-stranded DNA from this cDNA template, viral reverse transcriptase then uses its ribonuclease activity to degrade viral RNA. Two classes

of antiretrovirals have been developed to target HIV reverse transcriptase.<sup>9</sup>

Nucleoside reverse transcriptase inhibitors (NRTI) are analogs of the naturally occurring deoxynucleotides; thymidine, adenosine, guanosine, cytosine and cytidine (Table 68.2). All NRTIs undergo intracellular phosphorylation by cellular kinases to their active triphosphate forms. During viral reverse transcription, they compete for incorporation in expanding viral DNA chains. All NRTI compounds lack a 3'-hydroxyl group on the deoxyribose moiety, which prevents further addition of nucleotides to the growing DNA chain, causing chain termination and thereby inhibiting viral replication.

In contrast, the non-nucleoside reverse transcriptase inhibitors (NNRTI) bind to a nonactive site on HIV reverse transcriptase, competitively inhibiting the enzyme and preventing the normal movement of the protein domains required for DNA synthesis.

**Integration:** Integration of transcribed viral DNA into the host genome is mediated by the viral integrase enzyme, a 32kDa protein encoded by the integrase portion of the viral *pol* gene. HIV integrase consists of three domains: an N-terminal zinc finger domain that enhances multimerization and promotes

**Table 68.2:** Reverse Transcriptase Inhibitors Classified by Target Nucleotide Analog

Class	Purine		Pyrimidine	
	Adenosine	Guanine	Cytosine	Thymidine
Endogenous nucleotide				
Synthetic NRTI analogs	Didanosine (ddI)	Abacavir (ABC) (carbovir)	Zalcitabine (ddC)	Zidovudine (AZT)
	Adefovir (PMEA)		Lamivudine (3TC)	Stavudine (d4T)
	Tenofovir disoproxil fumarate (TDF)		Emtricitabine (FTC)	

integration of the two ends of viral DNA into the host cell chromosome, a dimeric central catalytic domain that is required for the enzymatic activity of HIV integrase, and a C-terminal domain that directs DNA binding.

Integrase binds to the viral DNA, creating a preintegration complex, and cleaves two nucleotides from the 3'-hydroxyl end of the viral DNA, exposing active chain ends. This preintegration complex then migrates to the host cell nucleus where HIV integrase cleaves the host DNA allowing the host and viral DNA to bond, resulting in strand transfer of the viral DNA into the host genome. Raltegravir is an HIV integrase inhibitor that interrupts integrase activity by binding to the catalytic domain and preventing strand transfer.<sup>10</sup>

**Virion Assembly and Maturation:** After integration, HIV provirus may lie latent within cells or undergo transcription into messenger RNA. At present, there is no effective treatment to remove latent virus from within cells and it therefore serves as a reservoir for persistent infection. Once a cell begins active viral RNA transcription, distinct splicing patterns result in either multiply-spliced variants that are transcribed into the regulatory proteins *nef*, *tat*, and *rev*, or single, unspliced transcripts which are either transcribed into the structural and enzymatic transcripts *pol* and *gag* or remain untranscribed to form new viral RNA particles. Together with host cell factors, these various components assemble into mature virions that are released from infected cells. These virions remain non-infectious until *gag* protein is cleaved into constituent proteins including the p24 capsid protein by the HIV protease, which infers infectivity on the virion. The HIV protease is an aspartyl protease and is a target for the protease inhibitor class of antiretroviral drugs, which bind to the active site of the HIV protease, disabling the enzyme and rendering virions noninfectious.<sup>11,12</sup>

## General Principles of Pharmacokinetics and Pharmacodynamics

In order to understand pharmacological issues specific to antiretroviral agents and particularly their use in combination, it is useful to review basic principles of pharmacology.

### PHARMACOKINETICS

Pharmacokinetics describes interactions between the host and a drug, principally related to processes of absorption, distribution, metabolism, clearance, and elimination. Exploration of these processes provides information relating to the bioavailability of the drug, the degree of protein-binding and the volume of distribution, the peak and trough drug concentrations in the blood (i.e., the  $C_{\max}$  and  $C_{\min}$  values), and the elimination half-life ( $t_{1/2}$ ) of the drug as well as the total systemic exposure to a particular drug estimated from the area under the concentration/time curve (AUC).

After oral administration, absorption of a drug depends on factors such as the drug formulation, gastric pH and emptying, gastrointestinal motility, perfusion of the absorptive surface

and the expression of transporters in the enteric surface such as P-glycoprotein. Different formulations of the same medication can result in significantly differing pharmacokinetics, as illustrated by the protease inhibitor lopinavir/ritonavir. Initially a soft gelatin capsule given as three capsules twice daily (BID) (133/33 mg) required dosing with food, but this when changed to a melt extrusion tablet formulation and taken two tablets BID (200/50 mg) showed sufficient increases in  $C_{\max}$  and AUC and lessened the need for dosing with food.<sup>13</sup>

Gastric pH is also important in the absorption of certain antiretrovirals, particularly the protease inhibitor atazanavir, the AUC of which is decreased by more than 75% in the presence of proton pump inhibitors and therefore, should not be coadministered.<sup>14</sup>

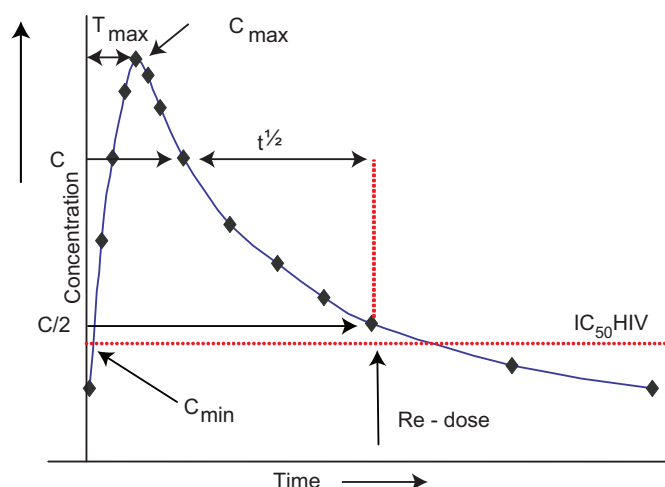
The volume of distribution is the relationship between the total amount of drug in the body and its concentration in the plasma and it is defined as the total amount of drug in the body/plasma concentration of the drug. The volume of distribution is influenced by the extent of plasma protein-binding and by physiological states. An increase in body fluid volume resulting from renal failure and a decrease in plasma proteins seen in liver failure can both increase the volume of distribution, while it is decreased with excess fluid loss seen with burns or with dehydration.

Protein-binding of drugs, to either albumin or  $\alpha$ -1-acid glycoprotein, involves complex interactions whereby the bound drug is slowly released from the binding protein at a rate determined by several physiological and competitive processes, including presence of other drugs competing for binding to the same protein. As only the unbound active free drug can cross through biological membranes reaching target receptors or be available for renal elimination, altered protein-binding may affect the therapeutic action of drugs or significantly alter its elimination half-life. Protein-binding varies significantly with antiretrovirals with the non-nucleoside reverse transcriptase inhibitors being highly protein bound.

### Pharmacokinetic Drug Concentration: Time Curve

Important pharmacokinetic parameters are estimated by measuring the concentration of the drug at various time points during the dosing schedule (Fig. 68.2). The peak drug concentration reached following drug administration is termed the  $C_{\max}$  and corresponding time is termed  $T_{\max}$ . Both parameters are intrinsically governed by the rate of drug absorption. After reaching the  $C_{\max}$ , the concentration of the drug gradually declines, with the elimination half-life ( $t_{1/2}$ ) being the time taken for the plasma drug concentration to fall by 50%. Most drugs follow "first-order" kinetics, where the rate of elimination is constant over time (Fig. 68.2). Mathematically the elimination half-life is determined by both the volume of distribution ( $V_d$ ) and the clearance (Cl) with the relationship defined by the equation  $t_{1/2} = 0.693 \times V_d / \text{Cl}$ . Changes in either the clearance or the volume





**Fig. 68.2:** The pharmacokinetic concentration: time curve.  $C_{\min}$  = minimum plasma concentration;  $C_{\max}$  = maximum plasma concentration.  $T_{\max}$  = time to reach maximum concentration;  $t_{1/2}$  = elimination half-life, estimated as the time for the drug concentration to fall by 50% during the elimination phase (provided that drug metabolism follows first-order kinetics;  $IC_{50}$  = concentration of drug required to inhibit 50% of viral replication in vitro. With the majority of antiretroviral medications it is desirable to re-dose before the plasma concentration of the drug reaches the  $IC_{50}$ .

of distribution of a drug may result in a significant change in the elimination  $t_{1/2}$ . Total body clearance is the volume of plasma cleared per unit time and is a function of the dose and the area under the concentration:time curve (dose/AUC).<sup>15</sup>

The “area under the curve” (AUC) of the concentration/time curve provides an indication of the bioavailability of a drug. As such, this can be altered by changing the dose, absorption or clearance of a drug. As a drug is cleared, the concentration will fall to a level at which redosing should occur. This concentration is termed the  $C_{\min}$  and is the minimum concentration in the dosing interval. This usually occurs prior to the subsequent dose although, depending on absorption properties of the drug, the concentration may continue to fall for a short time after administration of the next dose before adequate absorption occurs. Pharmacokinetic characteristics of commonly used antiretroviral agents are outlined in Table 68.3.

As many pharmacokinetic properties of drugs involve interactions with biological systems, there is unsurprisingly significant inter-individual variability in drug concentrations, arising from differences in absorption, distribution, metabolism and elimination between individuals. The contribution of host genetics to these processes is increasingly recognized. Pharmacogenomics may help explain some extreme variability within certain individuals, mostly exhibited through genetic

**Table 68.3:** Pharmacokinetic Properties of Common Antiretroviral Agents

Drug class	Drug name	MW (Daltons)	EC <sub>50</sub> (nM)	C <sub>min</sub> (ng/ml)	C <sub>max</sub> (ng/ml)	AUC (ng·h/ml)	Half-life (hrs)	Protein binding (%)
NRTI	Abacavir	670.76	3700–5800	NA	4260±1190	11950±2510	1.45±0.32	50
	Lamivudine	229.3	3700–5800	NA	2040±540	8870±1830	5–7	<36
	Tenofovir	247.24	1.3–6400	NA	300±90	2290±690	17	<1
	Emtricitabine	247.24	1.3–640	90	1800±700	10000±3100	10	<4
	Stavudine	224.2	9–4000	8±9	536±146	2568±454	2.3	<5
	Zidovudine	267.24	10–490	NA	NA	1400±200	0.5–3	<38
NNRTI	Efavirenz	315.67	1.7–2.5*	1767±1010	4072±1168	58083±23044	40–55	>99
	Nevirapine	226.3	90	4500±1900	NA	NA	20–35	60
	Etravirine	453.28	0.9–5.5	297±391	NA	4522±4710	41	99.9
PI	Atazanavir/r	802.9	2–5	273±298	3152±2231	22262±20159	6.5	86
	Darunavir/r	593.73	1.2–8.5	3578±1151	NA	62349±16143	15	95
	Lopinavir/r	720.95	10–27	7100±2900	9800±3700	92600±36700	NA	98–99
	Amprenavir/r	505.64	130–800	280 (120–510)	5360 (920–9810)	18460 (3020–32950)	7.1–10.6	90
	Saquinavir/r**	670.86	1–30	371 (245–561)	2477Ψ	29214	NA	97
Integrase Inhibitors	Raltegravir	482.51	31±20*	69	NA	6900	9	83
Entry inhibitors	Enfuvirtide	4492	0.089–107	3300±1600	5000±1700	48700±19100	3.8±0.6	92
CCR5 antagonists	Maraviroc	513.67	0.1–4.5	60	287	1865	14–18	76

\* EC<sub>90-95</sub> data presented.

\*\* Based on Invirase® formulation dosed at 1000/100 bid.

Ψ Data based on Fortovase® formulation.

AUC, area under the concentration:time curve; EC<sub>50</sub>, 50% effective concentration; C<sub>min</sub>, steady-state minimum plasma concentration after standard dosing; C<sub>max</sub>, steady-state maximum plasma concentration after standard dosing. MW, molecular weight; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; NA, not available. All parameters are derived from relevant drug product information booklets.

variations in cytochrome P450 (CYP450) isozyme metabolism arising from the presence of particular polymorphisms that may predispose an individual to either accelerated or reduced drug metabolism.

## PHARMACODYNAMICS

Pharmacodynamics describes the effect of the drug on the body. It is the relation between drug concentration and the pharmacological response in terms of efficacy. It also relates to drug concentration and the related toxic side effects. The desired range of concentration of a drug should produce effect without toxicity and is termed as the therapeutic range.

## Pharmacokinetics, Pharmacodynamics, and Antiretrovirals

In order to maintain constant suppression of viral replication, a sufficient plasma concentration of an antiretroviral must be sustained throughout the dosing interval. It is therefore important, particularly for drugs such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, that the  $C_{\min}$  never falls below a concentration required to maintain virological suppression. The concentration of drug necessary to suppress 90% or 95% of viral replication (the  $IC_{95}$ ) is estimated *in vitro*. During periods of nonadherence, or if drug interactions result in increased clearance of an antiretroviral drug, the  $C_{\min}$  may fall sufficiently to permit viral replication to recur, which can lead to treatment failure (termed virological failure) and the emergence of resistance (see below).

A significant number of antiretroviral agents undergo hepatic metabolism and induction or inhibition of the hepatic CYP450 enzyme system by PI, NNRTI and the CCR5 antagonist maraviroc may result in drug–drug interaction when used in combination. The specific isozymes affected by each drug are outlined in Table 68.4. Induction of the CYP450 enzyme systems increase plasma concentrations of the isoenzymes resulting in decrease in the plasma concentration of substrate drugs. The integrase inhibitor raltegravir is somewhat different as it is metabolized by the uridine diphosphate-glucuronosyl transferase A1 enzyme (UGT A1). Most NRTIs are renally eliminated, hence the lower propensity for drug–drug interactions within this class. The exceptions are zidovudine, which is metabolized via glucuronidation with minimal renal elimination, and the nucleotide RTI (NtRTI) tenofovir, which is actively secreted from renal tubular cells.

Enzyme induction can take up to 14 days to take effect. This complicates use of drugs which induce their own metabolism, such as the NNRTI nevirapine, which is therefore initiated at a lower dose for 2 weeks to enable enzyme induction after which a higher maintenance dose is required to maintain therapeutic plasma concentrations and antiviral efficacy.<sup>16</sup> In contrast, inhibition results in decreased metabolism and elimination of the substrate drug and results in prolonged  $t_{1/2}$ . The protease inhibitor ritonavir is a potent inhibitor of the CYP3A4 isoenzyme. This

**Table 68.4:** Antiretroviral Agents and Enzymes Involved in Their Transport and Metabolism

Drug class	Drug	Substrate	Inhibition	Induction
NNRTI	Efavirenz	3A4, 2B6		3A4, 2B6
	Etravirine	3A4, 2C9, 2C19	2C9, 2C19	3A4
	Nevirapine	3A4, 2B6		3A4
Protease inhibitor	Atazanavir	3A4, P-gp	UGT 1A1, 1A2, 3A4	
	Fosamprenavir	3A4, P-gp	3A4 ( <i>in vitro</i> )	3A4 ( <i>in vivo</i> )
	Darunavir	3A4, P-gp	3A4	
	Indinavir	3A4, P-gp	3A4	
	Lopinavir/ritonavir	3A4, P-gp	3A4	2C9, 2C19, 1A2
	Nelfinavir	2C19 (M8 → 3A4)	3A4	
	Ritonavir	3A4		
	Saquinavir	3A4, P-gp	3A4	
	Tipranavir		3A4, 2D6	1A2, 2C19
NtRTI	Tenofovir	MRP4		
Integrase inhibitor	Raltegravir	UGT 1A1		
CCR5 inhibitor	Maraviroc	3A4		

MRP4, multidrug resistance protein type 4; NtRTI, nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; P-gp, Transmembrane drug transporter P-glycoprotein; UGT, uridine diphosphate-glucuronosyl transferase. Other substrate codes denote isoenzymes of cytochrome P450 system. All parameters are derived from relevant drug product information booklets.

characteristic has been manipulated to increase the bioavailability of most other protease inhibitors by combining them with a small dose (baby dose) of ritonavir. By inhibiting metabolism, ritonavir increases the drug concentrations throughout a large dosing interval, thereby enabling lower pill burden and easier dosing schedule.<sup>17</sup>

Antiretroviral pharmacodynamics is complicated by the fact that the efficacy of most antiretrovirals is not measured directly through inhibition of a target viral enzyme, but indirectly through inhibition of viral replication. The main pharmacodynamic metrics in HIV therapy for efficacy are the HIV RNA quantification (either *in vitro* or *in vivo*) and increases in CD4 + T lymphocytes. Pharmacodynamic properties are further complicated by the fact that the antiretroviral drugs are used in combination, rendering it more difficult to determine the relevant pharmacodynamic properties of individual drugs within a combination. As a result, few clear dose–response relationships have been described for antiretrovirals. Similarly, as toxicities arising from antiretroviral exposure often do not relate to effects on inhibition of the target enzyme, but rather arise from non-antiviral effects of antiretrovirals on host biological processes (such as development of hepatic, renal,

or bone marrow dysfunction), these toxicities vary considerably and are often not related to either the dose or pharmacokinetic properties of the antiretrovirals. As a result, the utility of routine measurement of antiretroviral pharmacokinetic properties as part of routine care in HIV-infected patients is questionable.

However, pharmacokinetic and pharmacodynamic properties of antiretrovirals determine not only their effectiveness but also their propensity to cause virological failure and induce resistance in the setting of low-plasma drug concentrations. The potential for antiretroviral drugs to induce resistance upon treatment failure, particularly failure to first-line antiretroviral therapy, differs considerably between antiretroviral drug classes. These differences can be explained at least in part by the pharmacokinetic and pharmacodynamic characteristics of specific drugs.<sup>18</sup>

## HIV AND ANTIRETROVIRAL RESISTANCE

The high-replication rate of the HIV virus, (an estimated  $10^{10}$  copies of HIV virus is produced per day in the absence of suppressive therapy), together with a high-error rate during replication, leads to multiple mutations occurring during replication. Some of these mutations occur in genes that are targets of antiretroviral therapy (such as the reverse transcriptase gene) and may alter the amino acid sequence of the resulting protein, which can in turn alter the ability of the drug to inhibit the replication.<sup>19</sup> For example, a mutation in HIV reverse transcriptase gene that results in an amino acid substitution of methionine for valine at position 184 (M184V) enables a virus with this mutation to continue to replicate even in the presence of the NRTI lamivudine (3TC). This “replicative advantage” means that, in the presence of lamivudine alone, virus with M184V mutation will be able to replicate while wild-type virus will remain suppressed.<sup>20</sup>

Resistance can be measured in three main ways: using genotypic assays, phenotypic assays, or a combination of the two—the virtual phenotype. In the genotype test, HIV RNA is derived from plasma of a patient with suspected resistance and the sequence of the gene of interest is compared to the sequence of “wild-type” or fully sensitive virus. Genes commonly examined include sequences of the *pol* gene that encode HIV reverse transcriptase and HIV protease, and the *env* gene encoding the V3 loop of gp120. Presence of particular mutations will give rise to changes in amino acid composition of the resulting protein, which can result in resistance to a particular antiretroviral drug. By mapping these mutations, a genotypic assay can help predict drugs to which the virus has developed resistance or is still sensitive.<sup>21</sup>

A phenotypic assay involves culturing of a virus with particular resistance mutations and exposing it to individual antiretrovirals in order to determine if the drugs can inhibit viral replication and, if there is a reduced activity, what fold increase in  $IC_{50}$  is required to overcome resistance. This test has the advantage of being able to quantify the level of resistance induced by a particular mutation but has the disadvantage of taking a considerable time to perform and also being expensive.

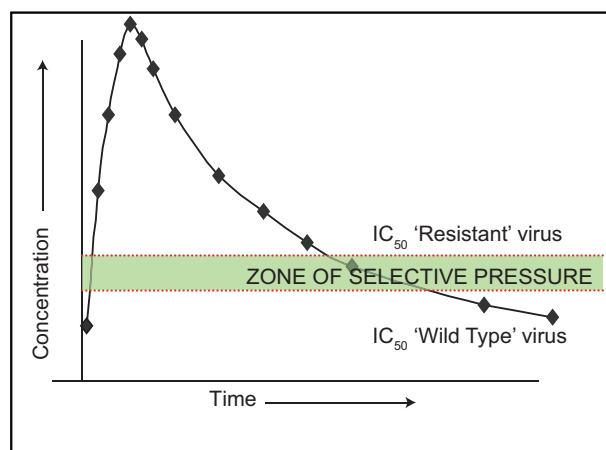
The virtual phenotype relies on comparing viruses with known mutations or groups of mutations to a database of phenotypic

test results of viruses known to harbor these mutations. This assay is much cheaper and, as it is comparative, is much quicker to perform than a phenotype test, but is dependent on the availability of archived data on the phenotypic characteristics of the virus under investigation.

With continued exposure to a drug, over a period the resistant virus will emerge as the predominant viral strain, leading ultimately to treatment failure. Emergence of resistance is prevented by using multiple drugs in combination, thereby making it more difficult for the virus to produce an increasing number of mutations required to render it resistant to multiple antiretroviral medications, and by ensuring that the concentrations of the drugs do not fall below a threshold where there is selective pressure on viruses harboring resistance mutations to replicate and become the predominant circulating viral species.<sup>22</sup> The range of drug concentrations in which resistant virus can replicate whilst wild-type virus remains suppressed is termed the “zone of selective pressure” (Fig. 68.3).

## ANTIRETROVIRAL RESISTANCE AND PHARMACOKINETICS

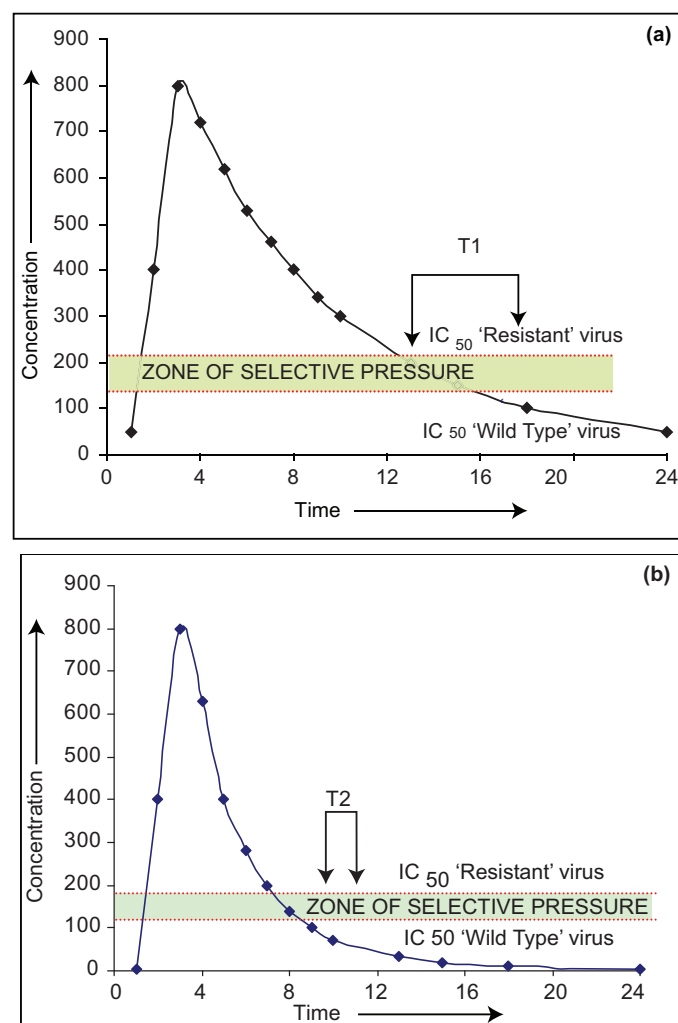
The pharmacokinetic properties of certain antiretrovirals may help explain the relative risk of resistance developing when drug concentrations fall. Patients failing antiretroviral regimens-containing drugs with longer half-lives, such as the NNRTI drug class and the integrase inhibitor raltegravir (Table 68.3), in which less resistance mutations are required to result in high-level resistance (termed a “lower genetic barrier” to resistance), tend to fail with drug resistance when compared to patients failing antiretroviral regimens-containing drugs with short half-lives and those that require multiple resistance mutations before high-level resistance occurs (a “high genetic barrier”), such as protease inhibitors.<sup>18</sup>



**Fig. 68.3:** Antiretroviral pharmacodynamics and resistance. The  $IC_{50}$  of a virus harboring resistance mutations may be higher than that of a wild-type virus, providing the resistant virus with a replicative advantage over the wild-type virus in conditions where the plasma concentration of an antiretroviral lies above that necessary to inhibit wild-type virus but below that necessary to inhibit resistant virus. This range of concentrations is termed the *zone of selective pressure*.



This is because with the use of drugs with short half-lives and high genetic barriers, the time during which the drug concentration remains within the zone of selective pressure remains short (Fig. 68.4a), so there is less time for the virus to develop the resistance mutations necessary to render the virus resistant and provide it with a replicative advantage over the wild-type virus. In contrast, in drugs with the longer half-lives and a lower genetic barrier, the time spent within the zone of selective pressure is considerably longer, giving more time for resistant mutations to arise while the wild-type virus remains suppressed (Fig. 68.4b). This is reflected in the higher number of patients failing NNRTI- or integrase-containing HAART with viruses harboring resistance mutations compared to patients failing ritonavir-boosted protease inhibitor-containing antiretroviral regimens.<sup>19,23</sup>



**Fig. 68.4:** Antiretroviral pharmacodynamics, elimination half-life and resistance. If taken intermittently, the plasma concentrations of drugs with longer elimination half-lives (a), such as non-nucleoside reverse transcriptase inhibitors and integrase inhibitors, spend more time in the 'zone of selective pressure' than drugs with shorter elimination half-lives (b), such as protease inhibitors, providing more opportunity for resistance mutations to emerge.

## ANTIRETROVIRAL RESISTANCE AND PHARMACODYNAMICS

Specific resistance mutations can result in very different changes in drug pharmacodynamics. The amount of additional drug required to suppress replication in a resistant virus (termed the "fold increase" in  $IC_{50}$  compared to wild-type virus) can vary greatly. The inhibitory quotient (IQ) provides a way to link this pharmacodynamic property to the pharmacokinetics of the specific drug. The IQ is the ratio between the  $C_{min}$  and the  $IC_{50}$  of either the wild-type or resistant virus ( $C_{min}/IC_{50}$ ), with a correction for protein-binding applied to translate *in vitro*-derived  $IC_{50}$  or  $IC_{95}$  values to *in vivo* drug concentrations (correction factor =  $IC_{50}/[\text{fraction free drug in vivo}]$ ).<sup>24</sup>

The inhibitory quotient can be very useful when presence of one or more mutations results in small, or step-wise increases in the fold change of the  $IC_{50}$  compared to wild type. Such an effect is seen with use of protease inhibitors, in which baseline IQ has been associated with subsequent virological response to therapy in treatment experienced patients, with a higher IQ expected to result in better drug potency. However, for drugs such as non-nucleoside reverse transcriptase inhibitors, where presence of single mutations can result in dramatic increases in  $IC_{50}$  (for example the K103N mutation is associated with a 20-fold increase in the  $IC_{50}$  of efavirenz), the clinical utility of the IQ is less clear, as the increase in drug necessary to suppress the resistant virus is not realistic at clinically used doses.

Two variations of the IQ have been used in clinical research: the virtual inhibitory quotient (VIQ) and the normalized inhibitory quotient (NIQ). The VIQ is calculated for by dividing a patient's  $C_{min}$  by the expected fold change in viral susceptibility (FC) obtained from a virtual phenotype of the virus under investigation, multiplied by the serum-adjusted control wild-type viral  $IC_{50}$  value ( $C_{min}/[FC \times IC_{50}]$ ) and the NIQ is derived by dividing an individual's IQ for a specific virus to the population IQ.<sup>25,26</sup> Both of these variations attempt to provide a more robust relationship between pharmacodynamics and pharmacokinetics for antiretroviral drugs and shown limited predictive value in determining treatment response to antiretroviral therapy, particularly in heavily pre-treated patients with resistant viruses.<sup>27</sup>

As the IQ relies on the  $C_{min}$  as the only pharmacokinetic parameter, this estimate presumes that inhibition of virological replication does not appreciably change at higher antiretroviral drug concentrations. However, *in vitro* research suggests that there is a dose-response relationship between antiretroviral drug concentration and the ability of HIV to infect new cells, that can be graphically depicted in a dose-response graph. The slope of this graph can be used to determine the instantaneous inhibitory potential (IIP) of an antiretroviral drug at specific concentrations, defined as the log reduction in single round infectivity at clinically relevant drug concentrations. For example, the IIP for  $C_{max}$  is derived from the equation,  $IIP_{C_{max}} = \log(1 + (C_{max}/IC_{50})^m)$ . Like the IQ, this equation incorporates both pharmacodynamic (the slope parameter "m" of the *in*

*vitro* dose–response curve and the  $IC_{50}$ ) and pharmacokinetic ( $C_{min}$ ) parameters (formula  $[IIPx = \log(1 + Cx/IC_{50})m]$ , where  $x$  = specific drug concentration). The IIP can potentially explain the superior performance of several antiretroviral drugs such as the PI atazanavir and darunavir and the NNRTI efavirenz in clinical trials, as they maintain an  $IIPC_{max}$  at 24 hours well above ( $>5 \log$ ) that required for viral inhibition.<sup>28,29</sup> However, which of the three measures described best predicts response still remains to be determined.

## Specific Antiretroviral Classes and Agents

This section provides a more detailed description of the currently available antiretroviral drug classes and the commonly used drugs within each class, outlining their mechanism of action, pharmacokinetic properties, adverse reactions, long-term toxicities, and important drug interactions.

### NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

The NRTIs are synthetic analogs of naturally occurring purine and pyrimidine analogs which act by competitive inhibition of HIV1 reverse transcriptase. With the exception of tenofovir disoproxil fumarate (TDF), the NRTIs are actually prodrugs requiring intracellular activation via a three-step phosphorylation

process that converts them to their active triphosphate form.<sup>30</sup> The *nucleotide* reverse transcriptase inhibitor TDF requires only two-step phosphorylation for activation. As previously described, HIV reverse transcriptase cannot distinguish NRTI triphosphates from their naturally occurring counterparts and their incorporation into growing viral DNA results in chain termination. Dual NRTI therapy, which forms the backbone of conventional HAART, comprises two agents related to differing purine or pyrimidine bases so as to avoid two drugs competing for incorporation for the same target base (Table 68.2). NRTIs also have the potential to inhibit host cellular DNA polymerases, including the mitochondrial DNA polymerase gamma (DNA pol-gamma). Tissue-specific inhibition of DNA pol-gamma by NRTI has been postulated to underlie many of the medium and long-term toxicities observed with NRTI use.

All the available NRTIs are available in oral formulations with oral bioavailability ranging from 25% to 90%. As only intracellular phosphorylated drugs are active, dosing schedules are not generally designed around the elimination half-life (Table 68.3). In general, plasma concentrations of NRTIs do not correlate with antiviral efficacy or toxicity as it is the rate of phosphorylation of the drug that is thought to determine activity.<sup>31</sup> Table 68.5 shows pharmacokinetic and pharmacodynamic characteristics of the available agents in the NRTI class.<sup>33–39</sup>

**Table 68.5:** Pharmacokinetic, Pharmacodynamic, and Treatment Characteristics of NRTI

Agent	Plasma $t_{1/2}$	Intracellular $t_{1/2}$	Oral bioavailability	Elimination	CSF:Plasma ratio	Common dosing	Comment
Zidovudine (AZT)	1.1	3	60%	Glucuronidation and renal excretion	0.5	300 mg BID	Toxicities include anemia and lipoatrophy
Didanosine (ddI)	1.6	25–40	30–40%	Renal excretion	0.21	Daily	Toxicities include lactic acidosis and lipoatrophy Use in combination with tenofovir results in lower CD4 <sup>+</sup> T-cell responses and higher virological failure rates
Stavudine (d4T)	1.0	3.5	85%	Renal excretion	0.39	40 mg BID	Linked with lipoatrophy, lactic acidosis, and peripheral neuropathy Dose reduction recommended if weight < 60 kg
Lamivudine (3TC)	3–6	12	83%	Renal excretion	0.12	Daily/ BID	FDC when combined with AZT
Abacavir (ABC)	1.5	24–60	83%	Metabolized by alcohol dehydrogenase and glucoronyl transferase Renal excretion of metabolite	0.3–0.44	Daily/ BID	Hypersensitivity in 4%—increased in HLA B*5701 positive recipients Linked with increased risk of myocardial infarction in some studies FDC when combined with 3TC Additional FDC when combined with both 3TC and AZT
Tenofovir disoproxil fumarate (TDF)	17	10–50	25–40% High-fat meal	Renal glomerular elimination and active tubular secretion	0.04 <sup>32</sup>	Daily	Can accumulate in renal tubular cells Rarely may cause renal failure, proteinuria, and Fanconi syndrome
Emtricitabine (FTC)	10	20	93%	Renal excretion	0.43	Daily	FDC when combined with TDF

BID, twice daily dosing; FDC, fixed-dose combination;  $t_{1/2}$ , elimination half-life; CSF, cerebrospinal fluid.

## Zidovudine

Zidovudine received approval from the US Food and Drug Administration (FDA) for treatment of HIV-1 infection in adults in 1987 and in infants over 3 months in 1990. It is available in several formulations, such as liquid (10 mg/ml), tablets (300 mg), capsule (100 mg), and suspension for IV injection (10 mg/ml). Zidovudine is metabolized by hepatic conjugation to an inactive glucuronidated metabolite and undergoes renal elimination, with clearance greatly exceeding creatinine clearance, indicating that significant tubular secretion takes place. Both renal and hepatic impairment may affect clearance of zidovudine.<sup>33</sup>

Zidovudine is effective in decreasing mother-to-child transmission (MTCT) of HIV. In the PACTG-076 study, maternal treatment with zidovudine during pregnancy and labor, and newborn administration in the first 6 weeks of life decreases MTCT by 70%. In neonates, zidovudine elimination is slower immediately after birth and then increases dramatically after the first week of life. This is important particularly in premature neonates when dosages must be decreased due to greatly decreased elimination.<sup>40</sup>

In addition to mitochondrial toxicity (discussed below), zidovudine may cause anemia secondary to bone marrow suppression. This can be a treatment limiting toxicity in some patients and is particularly problematic in resource limited settings where there is a high prevalence of helminth infection, which can also cause chronic anemia.<sup>41</sup>

## Lamivudine

Lamivudine is the negative enantiomer of a synthetic cytidine analog. In addition to anti-HIV-1 activity, it also has activity against HIV-2 and hepatitis B infection. It is available in liquid (10 mg/ml) and tablet (150 mg) formulations. Lamivudine is predominantly (70%) cleared unchanged in the urine, with clearance partly age dependant with dosages decreased in the first week of life. Lamivudine concentrations are increased in patients with moderate to severe renal impairment due to decreased clearance. Lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction.<sup>42</sup>

## Tenofovir Disoproxil Fumarate

As tenofovir disoproxil fumarate (TDF) is a nucleotide, it bypasses the initial rate-limiting phosphorylation step and is hydrolyzed by plasma esterases and then metabolized intracellularly to the active triphosphate form. It is available in 300 mg tablets. Its oral bioavailability is affected by coadministration with a high-fat meal with a 40% increase in AUC. Pediatric dosing studies have shown  $C_{max}$  and AUC values decreased by up to 30% in children taking adult capsules. Due to the anionic charge of the molecule, it is thought to have poor CSF penetration.<sup>36</sup>

Elimination of TDF is predominantly renal, with active renal tubular secretion via renal transport proteins OAT 1 and 3 and MRP4. In patients with renal failure, TDF can accumulate in renal

tubular cells and can rarely induce renal failure with a Fanconi's-type proximal tubulopathy (characterized by hypophosphatemia, proteinuria, aminoaciduria, and glycosuria) in patients without known pre-existing renal dysfunction.<sup>43</sup> Regular monitoring of renal function (creatinine clearance and dipstick urinalysis) is recommended for patients on TDF. Pharmacokinetics of TDF are not substantially altered in subjects with hepatic impairment.

## Emtricitabine

Emtricitabine (FTC) is a fluorinated analog of lamivudine, although it does have a longer elimination  $t_{1/2}$  than lamivudine and is available as a capsule (200 mg) and oral solution (10 mg/mL). Its longer half-life supports once-daily dosing, which has resulted in its use in fixed-dose combination (FDC) form with TDF (Truvada®) and with TDF and efavirenz (Atripla®). Like lamivudine, FTC is ineffective in viruses harboring a resistance mutation M184V/I in the reverse transcriptase gene, although the frequency of the M184V mutation in patients on FTC is lower than that seen in patients failing lamivudine-containing regimens.<sup>21</sup>

## Abacavir

Abacavir is a carbocyclic nucleoside available in liquid (20 mg/ml) and tablet (300 mg) formulations. It has a relatively high CSF:plasma ratio suggesting good CSF penetration with potential use in patients with HIV-associated central nervous system (CNS) disease. It is primarily metabolized by hepatic glucuronidation and carboxylation. It is a substrate for P-glycoprotein and undergoes hepatic metabolism, although avoiding the CYP system. However, its metabolism may be affected in patients with moderate to severe hepatic impairment. Use of abacavir has been linked to the development of a hypersensitivity reaction (HSR), which occurs predominantly in patients carrying the HLAB\*5701 allele (see section on Antiretroviral Toxicities below).<sup>35</sup>

## NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

This class of drugs can be roughly classified into the first generation NNRTIs, efavirenz, nevirapine, and delavirdine (an older NNRTI which is no longer in use) and the second generation NNRTIs, etravirine and rilpivirine (TMC278, which is still in clinical trials). NNRTIs bind non-competitively to the p66 subunit of HIV-1 reverse transcriptase at a hydrophobic pocket distant to the active site of the enzyme, inducing a conformational change that alters the active site, decreasing the ability of naturally occurring nucleotides to bind. This inhibits cDNA elongation and halts viral replication.

Although effective, first generation NNRTIs have a low genetic barrier to resistance, and cross-resistance to all first generation NNRTIs can result from the presence of a number of single mutations in HIV reverse transcriptase. The second generation NNRTIs retain antiviral activity in the presence of some of these mutations, although their efficacy decreases considerably



**Table 68.6:** Pharmacokinetic, Pharmacodynamic, and Treatment Characteristics of NNRTI<sup>16,44–47</sup>

Drug	Plasma $t_{1/2}$	Oral bioavailability	CSF:Plasma ratio	Dosing	Comment
Efavirenz	45	/a	0.61	600 mg/day	Available as FDC with TDF and emtricitabine (Atripla®) Associated with CNS side effects
Nevirapine	25–30	93%	0.63	200 mg BID or 400 mg/day	Can cause hepatotoxicity when initiated with high CD4 <sup>+</sup> T-cell counts Rash common
Etravirine	41	Not established	No data	200 mg BID	Less interactions with methadone Significant interactions with some protease inhibitors and maraviroc

BID, twice daily dosing; FDC, fixed-dose combination;  $t_{1/2}$ , elimination half-life; CSF, cerebrospinal fluid.

with accumulation of NNRTI-resistant mutations. Etravirine, in particular, is a highly flexible molecule and may alter or rotate within the binding site to allow multiple-binding conformations in the presence of pre-existing resistance mutations.<sup>9</sup>

Both efavirenz and nevirapine induce the hepatic CYP 450 system, giving rise to multiple potential drug–drug interactions. NNRTIs are generally heavily protein bound but have good CNS penetration (Table 68.6).<sup>16,44–47</sup>

## Efavirenz

Efavirenz is recommended in first-line HAART regimens for ARV-naïve patients in most treatment guidelines.<sup>48</sup> Like the other NNRTIs, it has an extended elimination half-life (Table 68.3) favoring once-daily dosing. Although it is highly protein bound (approximately 99%), the free fraction penetrates the CSF with a CSF/plasma ratio of 0.61. Efavirenz undergoes hepatic elimination predominantly via CYP2B6 and to a lesser extent through CYP3A4 metabolism. The AUC is significantly increased (28%) when dosed with high-fat meals; therefore, it is recommended to be taken on an empty stomach.<sup>44</sup>

Efavirenz induces CYP3A4 metabolism and can therefore interact with drugs metabolized via this pathway. It also induces its own metabolism, with steady state pharmacokinetics reached after approximately 14 days therapy. As it undergoes hepatic metabolism, efavirenz should be used with caution in patients with mild to moderate liver disease and is contraindicated in patients with severe hepatic impairment. As less than 1% of efavirenz is excreted unchanged in the urine, the impact of renal impairment on efavirenz elimination should be minimal. Its use in pregnancy is controversial, as first trimester exposure in animals was associated with development of neural tube defects.<sup>44</sup>

Although rash is commonly observed after initiation of efavirenz, it is often mild and may resolve without discontinuing treatment. Rarely severe rash will occur, necessitating treatment discontinuation. The principal toxicity of efavirenz is in the central nervous system (CNS), with symptoms ranging from insomnia, dizziness and vivid dreams to frank psychosis and depression. These side effects are most prevalent within the first 2 weeks after treatment initiation, probably reflecting higher circulating plasma concentrations in the days preceding full

auto-induction of metabolism and establishment of steady state plasma concentrations.<sup>49</sup> However, a case:control study examining development of CNS side effects in patients initiating efavirenz-containing HAART showed that efavirenz plasma concentrations were not significantly different in those developing CNS side effects versus those who did not.

However, specific polymorphisms in the *CYP2B6* gene affect efavirenz metabolism as this is the primary metabolism pathway for efavirenz. The *CYP2B6* gene is highly polymorphic and single nucleotide polymorphisms resulting in varying genotypes have been shown to result in elevations in peak plasma concentrations and are associated with increased CNS side effects. Several polymorphisms have been implicated, including G516T and G83T polymorphisms. Polymorphisms at the G516T position gives rise to GG wild-type genotype, GT heterozygous, and TT homozygous genotypes, homozygosity for TT, found only in African-American patients in one study, resulted in significantly increased AUC and plasma concentrations of efavirenz in excess of 6000 ng/ml. Dose reduction from 600 mg daily to 400 mg daily in patients carrying these polymorphisms may reduce CNS side effects while maintaining sufficient target  $C_{min}$  concentrations.<sup>49–51</sup>

Although the efficacy of such an approach in patients with CNS side effects without these polymorphisms has not been formally investigated, during the drug development of efavirenz there was no difference in efficacy between different doses evaluated at phase II, which included a dose of 400 mg daily, but the higher dose of 600 mg daily was chosen for investigation in phase III clinical trials. The main phase II trial of efavirenz, DMP-005, showed similar efficacy of 400 mg once daily compared to 600 mg once daily and was shown to have less CNS side effects. In addition to the potential for less side effects, dose reduction would lead to an approximately 30% reduction in the cost of efavirenz. The ENCORE 1 trial aims to compare the efficacy and safety of first-line treatment with efavirenz at the standard 600 mg once-daily dose versus the 400 mg once-daily dose in 600 patients.<sup>52</sup>

## Nevirapine

Nevirapine is a dipyrindodiazepinone, structurally related to the benzodiazepines. Its bioavailability is independent of

food intake and its long half-life supports once-daily dosing. Like efavirenz, nevirapine is metabolized by and induces the CYP450 enzyme system, predominantly through CYP3A4 with some involvement of CYP2B6. It also induces its own metabolism within the first 2 weeks of therapy and is initially used at a reduced dose of 200 mg daily, raising to 400 mg daily after 2 weeks of therapy.<sup>16</sup>

Toxicity associated with nevirapine focuses on hypersensitivity reaction and hepatotoxicity. These reactions are most likely to occur within the first 8 weeks of treatment, with hepatotoxicity in particular observed in patients initiating nevirapine-containing HAART at higher CD4<sup>+</sup> T-cell counts. As a result, nevirapine should be avoided in antiretroviral naive patients with CD4<sup>+</sup> T-cell count is >250 cells/ $\mu$ L in women and >400 cells/ $\mu$ L in men. Rash is common, occurring in approximately 10% patients and should be closely monitored as it may accompany a more severe hypersensitivity reaction, in which case the drug should be discontinued.<sup>16,53</sup>

## Etravirine

Etravirine was approved for use by the FDA in January 2008 for treatment-experienced HIV-infected patients. As food increases etravirine absorption and bioavailability, it is recommended to dose with or after a meal. It is available in an oral formulation at 200 mg twice daily. Like efavirenz and nevirapine, etravirine undergoes CYP450 metabolism, but to a lesser extent with >80% eliminated unchanged in the feces. As a result it causes less drug interactions than other NNRTIs.<sup>45</sup>

As a second generation NNRTI, etravirine is considered to have a higher genetic barrier to resistance as it is less susceptible to high-level phenotypic resistance with single mutations.<sup>54,55</sup> As different NNRTI resistance mutations will have varying effects on the efficacy of etravirine, several resistance mutation weighting scores have been developed that predict the efficacy of etravirine as a function of the number and position of resistance mutations found. Although the highest weighted resistance mutations include Y181I and Y181V, the commonest NNRTI mutation, K103N, does not feature in the weighting and is thought to have minimal impact on the efficacy of etravirine.<sup>56</sup> However, as etravirine has a prolonged  $t_{1/2}$ , there is still increased risk of development of virological failure with resistance during periods of nonadherence (see section on pharmacodynamics above).

Etravirine significantly interacts with other antiretrovirals. It decreases the  $C_{min}$  of the protease inhibitor atazanavir by up to 37% even in the presence of ritonavir boosting and decreases exposure to the CCR5 antagonist maraviroc by 53%, necessitating dose adjustment of maraviroc to 600 mg BID in the absence of concomitant administration of ritonavir within the regimen. In contrast, etravirine increases concentrations of the protease inhibitor fosamprenavir. Careful consideration of these complex interactions is required when constructing HAART regimens containing these agents.<sup>45,55</sup>

## IMPORTANT DRUG–DRUG INTERACTIONS WITH NNRTIs

### Methadone

Methadone replacement therapy, used in harm reduction initiatives in those with opiate addiction, has significant interactions with NNRTIs. Methadone metabolism is increased when coadministered with efavirenz or nevirapine with studies showing decreases in AUC of 52% and 46% for the S-enantiomer and R-enantiomer of methadone, respectively. Clinically, this can precipitate symptoms of methadone withdrawal. Although this can be managed with close monitoring and increasing the methadone dose, there is the added danger of methadone toxicity, which can be life-threatening, if the patient undergoes periods of unscheduled treatment interruptions or nonadherence, both of which are common in HIV-infected injecting drug users. Plasma concentrations of buprenorphine, an alternative opiate substitute, are also reduced by both efavirenz and nevirapine. In contrast, etravirine does not appear to have any clinically significant impact on methadone concentrations.<sup>57,58</sup>

### Rifampicin

The antimycobacterial drug rifampicin is a potent inducer of the CYP450 enzyme system and can decrease the AUC of efavirenz by approximately 20%.<sup>59</sup> Efavirenz is still recommended as a component of HAART in patients coinfecting with HIV and tuberculosis, with some guidelines recommending an increase in the dose of efavirenz from 600 mg daily to 800 mg daily in patients weighing over 60 kg when coadministered with rifampicin. In contrast, coadministration of nevirapine with rifampicin results in increased rates of virological failures, likely related to decreases in plasma concentrations of nevirapine and therefore the two drugs should not be used in combination.<sup>44</sup>

## PROTEASE INHIBITORS

Protease inhibitors represent a potent class of antiretroviral agents that are attractive due to their relatively high genetic barrier to resistance coupled with virological efficacy that in some cases is comparable to the NNRTI efavirenz.<sup>60</sup> Protease inhibitors are mostly lipophilic organic bases and are generally highly protein bound (Table 68.3 and Table 68.7). As most are metabolized through the CYP450 pathway, there is significant potential for drug–drug interactions.<sup>61</sup>

### Ritonavir

Although ritonavir has antiviral efficacy, it is now overwhelmingly used in clinical practice as a pharmacological booster of other drugs, principally other protease inhibitors. Its use as a PI in its own right was limited by intolerance, largely GI side effects and extreme dyslipidemia, and large pill burden. It is available in capsule (100 mg), tablet (100 mg), and liquid formulation (600 mg/7.5 mL). Ritonavir capsules require refrigeration; however,

**Table 68.7:** Pharmacokinetic, Pharmacodynamic, and Treatment Characteristics of PIs

Drug (ritonavir boosted)	Plasma $t_{1/2}$	Oral bioavailability	Dose	CSF/Plasma ratio
Atazanavir	8.6	68%(2)	300 mg/day*	0.002–0.023
Darunavir	15	82%	600 mg BID or 800 mg/day	
Lopinavir	5–6	N/A	2 tablets BID**	Not detected
Fosamprenavir	15–23	N/A		Negligible
Tirpanavir	5.5	N/A	500 mg BID	N/A
Saquinavir	7–12	4% extensive 1st pass metabolism	1000 mg BID	Negligible
Indinavir	2	62%	800 mg BID	

\*Can be dosed at 400 mg/day in the absence of ritonavir boosting.

\*\* Coformulated with ritonavir.

BID, twice daily dosing; N/A, data not available;  $t_{1/2}$ , elimination half-life; CSF, cerebrospinal fluid.

the melt extrusion tablet formulation, introduced in 2010, does not require refrigeration. Overall bioavailability of ritonavir is 60–80% and is almost entirely protein bound at 99%.<sup>17</sup>

Ritonavir is a powerful inhibitor of the CYP3A4 isozyme and it is this property which is exploited in order to pharmacologically enhance exposure of other antiretrovirals metabolized by CYP3A4, specifically other protease inhibitors, resulting in decreased dosing requirements and longer dosing intervals. However, potent inhibition of the CYP3A4 gives rise to multiple drug–drug interactions. Ritonavir inhibits other drug transport proteins and efflux pumps including the multi-drug resistance transporters MDR1 (also known as P-glycoprotein) and MDR2 of which other PI as well as many other drugs are substrates.<sup>62,63</sup>

Common drugs that interact with PI include HMG-Co A reductase inhibitors (commonly known as statins) fluticasone, an inhaled corticosteroid, and phosphodiesterase inhibitors used in erectile dysfunction.<sup>48</sup> Systemic exposure of statins, especially simvastatin, which is metabolized by CYP3A4, is greatly increased in the presence of ritonavir, increasing the potential for statin-induced hepatotoxicity or myositis. Concomitant use of ritonavir with fluticasone nasal spray results in 350-fold increase in the AUC and 25-fold increase in the  $C_{max}$  of fluticasone, which can lead to steroid toxicity and Cushing syndrome in some patients. Additionally, discontinuation of ritonavir in this setting can result in severe Addisonian symptoms due to relative steroid withdrawal. Coadministration of ritonavir results in an 11-fold and 49-fold increase in exposure to the phosphodiesterase inhibitors sildenafil and vardenafil respectively and a fourfold increase in the AUC of rifabutin, an antimycobacterial drug.<sup>17,61</sup>

## Atazanavir

Atazanavir has an elimination half-life that favors once-daily dosing and is usually dosed at 300 mg daily with 100 mg ritonavir, although it can also be used “unboosted” at a daily dose of 400 mg. It is metabolized via CYP3A4 and is also a potent inducer of P-gp in the enteric lumen. It is predominantly eliminated via the liver with very low renal clearance.<sup>64</sup>

Atazanavir inhibits UDP-glucuronyl transferase, resulting in elevations in circulating concentrations of unconjugated bilirubin in most patients, with scleral icterus occurring in a minority, necessitating treatment discontinuation in approximately 4% of patients. Elevations in bilirubin are not considered to be hepatotoxic and most treatment discontinuations arise due to cosmetic implications arising from icterus.<sup>65</sup>

The bioavailability of atazanavir is approximately 62% and is optimal at a lower gastric pH. Concomitant use of proton pump inhibitors (PPI) reduces the overall bioavailability of the drug and therefore concomitant use of atazanavir and PPI is contraindicated.<sup>14</sup> Although H<sub>2</sub> receptor antagonists can be used as an alternative to PPIs, these should be administered at least 10 hours after atazanavir is dosed. As described above, use of atazanavir in combination with the NNRTI etravirine is not recommended as atazanavir exposure is significantly reduced. Conversely coadministration of atazanavir and nevirapine results in increased nevirapine exposure and increased risk of toxicity.<sup>64,66</sup>

CSF penetration is poor, with one study suggesting median CSF concentrations with or without ritonavir of 10.3 (<5–21.1) ng/mL and 7.9 (6.6–22) ng/mL with one in four CSF samples having concentrations <5 ng/mL, below the estimated  $IC_{50}$  for atazanavir (approximately 1–11 ng/mL).<sup>66,67</sup>

## Darunavir

Darunavir is approved for use in both antiretroviral naive and treatment-experienced patients. It is dosed at 600 mg twice daily with 100 mg ritonavir and administered with food. It can also be dosed at 800 mg daily with 100 mg ritonavir in antiretroviral-naive patients. Darunavir absorption is dependent on P-gp protein transportation across the intestinal lumen and it is highly protein bound (approximately 95%). It undergoes hepatic metabolism through CYP3A4 and is a weak inducer of CYP2C9 with approximately 7% of the drug eliminated through the kidney.

As darunavir contains a sulfonamide moiety, it can cause allergy and rash in patients with a known sulfonamide allergy. Darunavir can be administered with etravirine despite decreases in etravirine AUC (37%) and  $C_{min}$  (49%), due to demonstrated clinical efficacy and safety of this combination in phase III clinical trials.<sup>68,69</sup>

## Lopinavir/Ritonavir

The lopinavir/ritonavir coformulated protease inhibitor (LPV/r) became available in 2000. It is the only PI in which ritonavir is



coformulated with another protease inhibitor within the same tablet. The adult tablet formulation contains lopinavir 200 mg and ritonavir 50 mg per tablet and can be dosed with or without food. The usual dose is two tablets twice a day. A liquid formulation of LPV/r (400 mg lopinavir/100 mg ritonavir per 5 ml) is also available, the usual dose being 5 ml twice daily with food. In addition to twice-daily dosing, once-daily dosing of LPV/r (four tablets) is an additional option in antiretroviral-naïve patients, although one study suggests that twice daily is still preferred in patients with high baseline HIV RNA >100,000 copies/ml. Once-daily lopinavir/ritonavir is not recommended in treatment-experienced patients and pregnant women.<sup>48,70</sup>

Lopinavir undergoes almost exclusive hepatic metabolism via CYP3A4 with renal elimination accounting for less than 3%. Moderate hepatic impairment (Child-Pugh B) increases lopinavir exposure by up to 30%.

Common side effects of LPV/r include gastrointestinal upset, diarrhoea, and dyslipidemia. With previous capsule formulations of LPV/r, diarrhea was more severe when dosed once daily. Although one small study suggested higher rates of diarrhoea with once-daily tablet dosing, a larger trial of 664 patients demonstrated similar rates of gastrointestinal side effects and virological suppression with once-daily and twice-daily dosing regimens.<sup>3</sup> Antiretroviral dyslipidemia will be discussed later in this chapter.

## Fosamprenavir

Fosamprenavir, a pro-drug of amprenavir, has a more favorable pharmacokinetic profile than amprenavir, allowing decreased pill burden and potential for twice-daily or once-daily dosing. It can be dosed in several regimens comprising either 1400 mg daily or 700 mg twice daily when boosted with ritonavir or 1400 mg twice daily when administered without ritonavir.

Fosamprenavir is hydrolyzed to active amprenavir by hydrolysis within gut epithelium. It is largely protein bound and undergoes hepatic metabolism via CYP3A4 with minimal renal elimination. As exposure to amprenavir increases considerably with hepatic impairment, dose reduction is recommended in those with hepatic dysfunction. Toxicities include rash (fosamprenavir contains a sulfonamide moiety), hepatitis and diarrhoea.<sup>34</sup>

## Other Protease Inhibitors

Although indinavir was one of the first PI approved for use, it is now no longer preferred in first-line HAART because of tolerability issues and heavy pill burden. Like other PIs, it is metabolized via the CYP3A4 system and is dosed at 800 mg twice daily with ritonavir boosting. Principal toxicities include renal dysfunction secondary to crystallopathy, presenting as crystaluria, nephrolithiasis, and renal angle pain with symptoms seen in up to 42% of treated patients. Hydration of 150 ml/hr throughout the day is recommended to avoid formation of renal crystals.<sup>71</sup>

Similarly, nelfinavir is another PI that is no longer recommended in first-line management of HIV infection largely due to a lack of

potency when compared to other antiretrovirals and intolerance principally diarrhoea.

## ENTRY INHIBITORS

### Maraviroc

Entry of HIV virus into cells requires interaction between the virus and cellular chemokine co-receptors, either CXCR4 or CCR5. Circulating viruses can be termed CCR5 tropic, CXCR4 tropic or mixed tropic depending on the predominant co-receptor used by circulating virus or sequences of the V3 loop of gp120. Maraviroc is an allosteric reversible inhibitor of the CCR5 co-receptor, approved for use in both treatment-experienced and treatment-naïve patients who are infected with CCR5-tropic HIV virus.<sup>48,72</sup> It binds to the transmembrane co-receptor cavity, which prevents interaction of the V3 loop of viral gp120 with the CCR5 co-receptor, thus preventing viral entry.<sup>73</sup> Additional antiviral effects include the inhibition of syncytia formation (fusion between infected and uninfected CD4<sup>+</sup> T-cells) and blockade of gp120-induced apoptosis.<sup>7,74</sup>

Maraviroc is available in 150 mg and 300 mg tablet with variable dosing (see below) has an oral bioavailability of approximately 33% and is 76% protein bound. It is metabolized by CYP3A4 with P-gp transportation in addition to significant renal elimination, accounting for almost 25% of total drug elimination, although in the presence of strong CYP inhibition this may be greater.

Maraviroc is a substrate for P-gp and CYP3A4 and is therefore subject to significant drug–drug interactions. As the AUC of maraviroc is related to antiretroviral efficacy, dosing of maraviroc varies considerably depending on which other drugs are used in the HAART combination (Table 68.8).<sup>75</sup>

Use of maraviroc is complicated by the requirement to identify circulating virus as being CCR5-tropic. Various tests have been introduced to help determine viral tropism, including cell-based infectivity assays and genotypic assays that sequence the V3 loop of the viral envelope glycoprotein gp120.<sup>76</sup> Virologic failure of maraviroc-containing HAART may be related to emergence of CXCR4 tropic virus or may result from development of resistant mutations within CCR5-tropic virus. Genotypic resistance to maraviroc arises due to mutations in the V3 loop.<sup>7,77</sup> Several distinct resistance mutations within the V3 loop region have been described in maraviroc treatment failures.<sup>7,74</sup>

### Enfuvirtide

Enfuvirtide (T20) is the only licensed fusion inhibitor class of antiretroviral agents. Fusion inhibitors prevent the final step of HIV entry into target cells. Binding of virus to the CD4 receptor and chemokine co-receptor induces conformational changes in the viral gp41 envelope protein, leading to translocation of the N-terminal fusion peptide of gp41 into the target cell membrane while the transmembrane anchor remains in the viral membrane. This “pre-hairpin intermediate” structure of gp41 is the target of enfuvirtide.<sup>78</sup>

**Table 68.8:** Maraviroc Dosing Recommendations: Dosing Schedules Dependent on Coadministered Antiretroviral Regimes and Medications

	Recommended maraviroc dose		
	150 mg Twice daily*	300 mg Twice daily	600 mg Twice daily
Concomitant medication	Atazanavir ± ritonavir	NRTIs	Efavirenz
	Darunavir/ritonavir	Nevirapine (without PIs except tipranavir/ritonavir)	Etravirine
	Lopinavir/ritonavir	Tipranavir/ritonavir	Rifampicin
	Fosamprenavir ± ritonavir	Enfuvirtide	
	Saquinavir/ritonavir	Raltegravir	
	Indinavir		
	Nelfinavir		
	Efavirenz + lopinavir/ritonavir		
	Efavirenz + saquinavir/ritonavir		
	Nevirapine + PI (except tipranavir/ritonavir)		

Enfuvirtide is a relatively large peptide comprised of 36 amino acids, necessitating administration by subcutaneous injection dosed at 90 mg twice daily. As it is administered subcutaneously, it has high bioavailability (>80%) and is 92% protein bound. It has poor CNS penetration, having a very low CSF:plasma ratio.<sup>79</sup> Its efficacy in heavily treatment-experienced patients was demonstrated in a number of studies, including the TORO-1 (USA) and TORO-2 (Europe and Australia)<sup>80</sup> trials and in the RESIST, MOTIVATE, BENCHMRK and POWER trials when used in combination with tipranavir, maraviroc, raltegravir, and darunavir, respectively.<sup>72,81–83</sup>

Enfuvirtide pharmacokinetics demonstrate large inter-patient variability, with low-plasma drug concentrations observed in some patients. Resistance can rapidly develop to enfuvirtide and, although resistant virus demonstrates reduced viral replicative capacity, there is no clinical benefit from continuing enfuvirtide in the setting of virological failure.

The major treatment-limiting side effect is injection site reactions which occur to a mild extent in the majority of patients but can be serious and treatment limiting in some cases.<sup>79,84</sup>

## INTEGRASE INHIBITORS

### Raltegravir

HIV integrase mediates incorporation of viral DNA into the host cell genome. Raltegravir is currently the only integrase strand transfer inhibitor licensed for use with efficacy demonstrated in the BENCHMRK (antiretroviral-experienced patients) and STARTMRK (antiretroviral naive patients) clinical trials.<sup>82,85</sup> Raltegravir is available in tablet formulation (400 mg), dosed at 400 mg twice daily. It is 83% protein bound with CSF:plasma ratios ranging from 0.01 to 0.61 (median 0.03) in one study. Raltegravir is metabolized via UGT1A1-mediated glucuronidation with no involvement of the CYP450 system, therefore reducing drug–drug interactions. However, strong inducers of UGT1A1 may affect raltegravir concentrations.<sup>86</sup>

Notably, raltegravir pharmacokinetic and pharmacodynamic studies have revealed no apparent relationship between either minimum or average raltegravir plasma concentrations and virological suppression. *In vitro*, inhibition of viral replication in infected cells exposed to raltegravir persists after removal of extracellular raltegravir, suggesting a persistent intracellular inhibition of HIV integrase, which some have referred to as a “post-antibiotic” effect. This may arise as a result of intracellular accumulation of raltegravir (similar to that observed with NRTI) and therefore a prolonged intracellular  $t_{1/2}$ .<sup>87</sup>

Like enfuvirtide, use of raltegravir in HAART combination that does not include other active agents results in a rapid loss of antiviral activity.<sup>88</sup> Raltegravir has a relatively low genetic barrier to resistance and, coupled with its prolonged  $t_{1/2}$ , results in increased virological resistance with treatment failure. In addition, there is evidence of substantial cross-resistance between raltegravir and other integrase inhibitors in development, such as elvitegravir (discussed below). The development of the Q148H and N155H point mutations in HIV integrase correlates with decreased efficacy of raltegravir, but with significantly reduced viral replicative capacity, with some arguing for continuation of raltegravir in an intensified antiretroviral regimen in heavily pre-treated patients with triple-class resistance.<sup>10,89</sup>

## ANTIRETROVIRAL DRUGS IN DEVELOPMENT

Several agents are in the latter stages of development and may add considerably to the antiretroviral armamentarium, promising to combine efficacy with the potential for new fixed-dose combinations to help improve adherence to treatment.

### Cobicistat

Cobicistat is a selective inhibitor of CYP3A4 that, unlike ritonavir, lacks antiretroviral activity. It may help replace ritonavir as the predominant pharmacological enhancer of other antiretroviral

drugs, namely, protease inhibitors and the second-generation integrase inhibitor elvitegravir (see below). Lack of antiretroviral activity and decreased propensity to cause dyslipidemia confers advantages of use of cobicistat over ritonavir, especially in HAART regimens that do not contain protease inhibitors. As it is highly water soluble, it can be coformulated with other antiretrovirals into fixed-dose combinations (FDC). Studies have shown that combinations containing cobicistat with atazanavir and the fixed-dose combination of TDF and FTC (Truvada®) compared with ritonavir-boosted atazanavir with Truvada have comparable virological efficacy and similar CD4+ T-cell responses. Early studies have, however, shown an increase in serum creatinine in patients receiving cobicistat, felt to be secondary to inhibition of tubular secretion of creatinine rather than an abnormality of glomerular filtration, as measured creatinine clearance was unchanged in those experiencing creatinine rises.<sup>90–92</sup>

### Elvitegravir

Elvitegravir is a second-generation integrase inhibitor, based on a modified quinolone antibiotic structure, with potent activity against HIV-1. HIV integrase has a single-binding site for magnesium, an ion required for strand transfer reactions and the assembly of integrase onto specific viral donor DNA fragments. By binding these magnesium cations, elvitegravir selectively inhibits the strand transfer reaction. Elvitegravir retains antiretroviral activity against multiple-drug-resistant HIV-1 *in vitro*. It is predominantly metabolized via CYP3A4 with minor metabolism occurring via glucuronidation using the UGT1A1 and UGT1A2 pathways. As such it is susceptible to boosting with both ritonavir and cobicistat, with pharmacokinetics supporting once-daily dosing. Maintenance of effective  $C_{min}$  concentrations is required for antiviral activity with a dose of 150 mg daily combined with ritonavir being explored in phase II and III clinical trials.<sup>10,93</sup>

Elvitegravir has been combined with cobicistat, tenofovir, and emtricitabine to produce a four-drug FDC—the “Quad” pill. In recent data, the quad pill demonstrated similar virological efficacy when compared to the three-drug FDC-containing tenofovir, emtricitabine and efavirenz (Atripla®), with fewer adverse events seen with the use of the quad pill, specifically efavirenz-associated CNS side effects.<sup>90</sup>

### Rilpivirine

Rilpivirine is an investigational, second-line NNRTI currently being studied in phase III clinical trials. It has strong binding properties and conformational flexibility that allows the drug to overcome mutations usually conferring NNRTI resistance such as the K103N mutation. However, it shares phenotypic cross-resistance with etravirine-associated resistance mutations. Rilpivirine pharmacokinetics differ significantly to etravirine in that its long elimination half-life of 38 hours favors once-daily dosing and potential coformulation into once-daily fixed-dose combinations. Its oral bioavailability is significantly increased with food and it is over 99% protein bound.

Rilpivirine is a substrate of CYP3A4 enzyme activity and is slowly metabolized in human hepatocytes through glutathione-dependent conjugative metabolism.<sup>94,95</sup>

The two phase III clinical trials, ECHO and THRIVE, compared rilpivirine with efavirenz when used with a NRTI backbone. Although 48-week data from both studies suggested non-inferior virological efficacy with rilpivirine-containing HAART, further analyses revealed more treatment failures related to tolerability in those on efavirenz-containing regimens (6.7% vs. 4.8% for efavirenz and rilpivirine-containing regimens respectively in pooled results) and more treatment failures related to virologic failure with rilpivirine-containing regimens (pooled results showing 9.0% vs. 4.8% virological failures in rilpivirine versus efavirenz-containing regimens, respectively).<sup>96</sup>

## Antiretroviral Toxicities

### MITOCHONDRIAL TOXICITY

All NRTIs inhibit cellular DNA polymerases of which HIV reverse transcriptase is one. NRTIs can also bind to other human DNA-polymerases, such as DNA polymerase-beta (necessary for repair of nuclear DNA) and mitochondrial DNA polymerase-gamma, which is exclusively responsible for the replication of mitochondrial DNA (mtDNA).

Mitochondrial DNA encodes for several polypeptides important in metabolic processes such as oxidative phosphorylation and the mitochondrial electron transport chain, which produces energy in the form of ATP. If NRTIs accumulate within the cells and are phosphorylated to their active forms, they are capable of disrupting mitochondrial function, leading to accumulation of reactive oxygen species, decreased tissue oxidative respiration, and increases in anaerobic respiration, resulting in increased production of lactic acid as a by-product.<sup>41,97</sup>

The range of toxicities resulting from NRTI-induced mitochondrial dysfunction tends to mirror the clinical features observed in inherited mitochondrial diseases and includes hepatic steatosis, lactic acidosis, myopathy, peripheral neuropathy, pancreatitis, and loss of peripheral adipose tissue (lipoatrophy). Each of these toxicities may occur in isolation or in various combinations, reflecting tissue-specific effects of NRTIs. This likely relates to the different affinities of specific NRTI for cellular kinases, which phosphorylate the NRTIs to their active forms. The activity of these cellular kinases differs significantly between tissues, resulting in accumulation of different NRTIs within specific tissues depending on specific cellular kinase activity within that tissue and the affinity of the drug for the specific kinase.<sup>48,98</sup>

Although inhibition of DNA Pol-gamma by NRTI, leading to mitochondrial DNA depletion and dysfunction, has been proposed to underlie many of these toxicities, mitochondrial dysfunction with exposure to NRTI has been observed both *in vitro* and *in vivo* in the absence of depletion of mitochondrial DNA, suggesting mechanisms other than inhibition of DNA pol-gamma through which NRTIs can cause mitochondrial dysfunction.<sup>97,99</sup>



## LACTIC ACIDOSIS AND HYPERLACTATEMIA

Lactic acidosis is a severe, life-threatening systemic form of mitochondrial dysfunction, seen mostly with the use of stavudine and didanosine but with cases described with use of most NRTIs.<sup>48</sup> It is a relatively rare presentation; in one randomized study of patients receiving combination NRTI backbone comprising ddI and d4T, the incidence of lactic acidosis was 3.2/1000 persons years of therapy. Most cases occur within the first 12 months after treatment initiation and women and those with higher body mass index are at higher risk of developing the condition.

Affected patients can present with rapid weight loss, nausea, tachypnea, malaise and abdominal pain with investigations revealing a metabolic acidosis, often with hepatic dysfunction. Management comprises discontinuation of antiretrovirals with supportive management of acidosis and end-organ dysfunction. Routine serum lactate measurement or measurement of mtDNA levels in peripheral blood have both been shown not to be predictive of the development of subsequent lactic acidosis and the mainstay of monitoring remains clinical vigilance to enable rapid identification of the onset of the condition.<sup>41</sup>

## LIPOATROPHY

Loss of subcutaneous adipose tissue is recognized as one of the major long-term side effects of antiretroviral therapy.<sup>100</sup> This largely irreversible process begins approximately 6 months after treatment initiation and those affected experience a selective, progressive loss of subcutaneous adipose tissue (with maintenance of muscle mass and stable or increasing visceral adiposity) as long as the causative antiretroviral agents are continued. Development of this clinical syndrome is associated with a dyslipidemia characterized by high total and LDL cholesterol, low HDL cholesterol and hypertriglyceridemia, and increased insulin resistance and a propensity to develop type 2 diabetes mellitus. These metabolic derangements may increase the risk of subsequent cardiovascular disease. The syndrome has been observed most with use of the thymidine analog NRTI zidovudine and stavudine and likely arises as a result of adipose tissue-specific mitochondrial dysfunction. The only partially effective management is discontinuation or substitution of thymidine analog NRTI.<sup>79,101</sup>

## LOW BONE MINERAL DENSITY

Initiation of antiretroviral therapy has been associated with decreases in bone mineral density (BMD), with greater decreases observed in those initiating regimens containing NRTI, especially TDF, and those initiating PI. The underlying pathogenesis is unclear but involves increases in bone turnover which seem to be self-limiting in the majority of patients, with BMD stabilizing in most patients 12 months after treatment initiation. Given the high prevalence of low BMD in HIV-infected patients, routine DXA imaging is recommended for post-menopausal patients,

patients over 50 year old, those with significant steroid exposure, a family history of hip fracture, and those with a history of fragility fracture, regardless of age or menopausal status.<sup>48,102</sup>

Although animal studies of TDF in monkeys using exposures of 6–12 times normal adult AUC values resulted in significant bone toxicity in 25% offsprings, there were no significant structural abnormalities. The effect of maternal or fetal exposure to TDF on bone turnover in infants of HIV-infected mothers is yet to be established.<sup>36,103</sup>

## ABACAVIR HYPERSENSITIVITY REACTION

Treatment with abacavir has been linked to a severe hypersensitivity reaction (HSR) characterized by fever, rash, myalgias, abdominal complaints, and hepatitis. In rare cases, usually upon re-exposure to abacavir, patients may experience life-threatening fulminant reactions, including development of Stevens-Johnson syndrome and fulminant hepatitis.<sup>35</sup> Most cases present within the first 6 weeks after initiation of abacavir, although confirmed cases have been described after significantly longer exposure. The risk of developing abacavir HSR is increased in those carrying the HLA B\*5701 allele, with the risk of development of abacavir HSR largely avoided by avoiding administration of abacavir to HLA B\*5701 positive patients. In the absence of HLA screening, where cases of abacavir HSR are suspected, abacavir should be permanently discontinued.<sup>104,105</sup>

## DYSLIPIDEMIA

Drugs within all three major antiretroviral drug classes, namely, NRTIs, NNRTIs and PIs, have the potential to induce dyslipidemia. The pattern of dyslipidemia differs between classes. Protease inhibitors induce a dyslipidemia characterized by high total and LDL cholesterol, decreased HDL cholesterol and elevations in triglycerides.<sup>106</sup> The extent of dyslipidemia varies significantly within the class, with more dyslipidemia observed with LPV/r than with newer boosted PIs such as atazanavir and darunavir.<sup>107,108</sup> The hypertriglyceridemia, particularly when combined with changes in adipose tissue distribution arising from lipoatrophy, is associated with increased insulin resistance and diabetes.<sup>109</sup> Dyslipidemia is at least partially reversible upon switching away from PIs while use of lipid lowering agents has limited benefit in the setting of ongoing PI exposure.

Efavirenz has been associated with elevations in total, LDL and HDL cholesterol, with nevirapine also associated with elevations in HDL cholesterol.<sup>110,111</sup> The resulting effect on cardiovascular risk is uncertain as the total:HDL cholesterol ratio remains relatively constant.

Within the NRTI class, elevations in LDL cholesterol have been demonstrated with use of stavudine, zidovudine, and abacavir, with additional increased insulin resistance also observed in patients on stavudine.<sup>112</sup> The extent of the elevations observed with NRTI use is generally smaller than those observed with PI or efavirenz.

## CARDIOVASCULAR DISEASE AND MYOCARDIAL INFARCTION

Increased rates of myocardial infarction (MI) have been observed in populations of HIV-infected patients and dyslipidemia induced by antiretroviral exposure is thought to play a role. In the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, a large prospective cohort study of >30,000 HIV-infected patients with cumulative exposure to certain protease inhibitors, including indinavir and LPV/r, the risk persisted after correction for dyslipidemia, suggesting an additional yet unexplained increased risk of MI with exposure to these drugs that is not explained by the dyslipidemia alone induced by their exposure.<sup>113,114</sup>

Association between antiretroviral exposure and myocardial infarctions is not limited to exposure to PIs. Exposure to abacavir has also been implicated in increased myocardial infarctions, although the data are conflicting. In the D:A:D study, current or recent exposure to abacavir was associated with approximately twofold increase in myocardial infarction, independent of other risk factors for cardiovascular disease.<sup>114,115</sup> Although several other cohort studies of patients, most of whom were on antiretroviral therapy with undetectable HIV RNA, also demonstrated a similar effect, randomized studies in patients initiating treatment have not shown similar increased rates, possibly related to confounding introduced by inflammation arising from uncontrolled HIV viremia.<sup>116</sup> Both inflammation and platelet dysfunction giving rise to prothrombotic states have been postulated as underlying mechanisms, although potential confounding by preferential use of abacavir in patients with renal dysfunction and illicit drug users, both of whom could have increased cardiovascular risk irrespective of abacavir exposure, have also been proposed as possible explanations for increased rates of myocardial infarction in abacavir recipients.<sup>117</sup>

## Therapeutic Drug Monitoring (TDM)

In therapeutic drug monitoring, plasma drug concentrations are used to individualize and optimize therapy either by guiding dose adjustments or to help explain unwanted treatment outcomes (either lack of efficacy or toxicity). Characteristics of drugs that make them amenable to TDM are outlined in Table 68.9.<sup>48,118</sup>

In HIV, TDM is predominantly used to ensure that adequate circulating antiretroviral concentrations are achieved and, in limited cases of toxicity, to ensure that drug concentrations are not too high, as seen with several polymorphisms in CYP 2B6 in patients prescribed efavirenz that result in very high plasma concentrations and increased CNS side effects.<sup>119</sup>

There are several current indications for TDM of antiretrovirals:<sup>48</sup>

- To ensure adequate plasma concentrations of drugs in patients prescribed multiple medications with potential for drug–drug interactions.
- To explain lack of expected antiviral efficacy after treatment initiation, potentially important in pediatric and pregnant patients where drug metabolism may be significantly altered.

**Table 68.9:** Characteristics of Drugs that Favor the Use of Therapeutic Drug Monitoring

Characteristics	Measures
Plasma drug concentrations should correlate with outcome, either efficacy and/or toxicity	Dose/response relationship or curve Dose/toxicity relationship or curve
The drug should have a clear therapeutic index	Normal range of values identified Low (efficacy) or high (toxicity) concentration values identified
Measurement of drug concentrations within a specific dosing interval should be reproducible	Low intra-patient variability in drug concentration measurements TDM assay should have a low inter-test variability
There must be considerable inter-patient variability in drug concentrations	Some measures will fall within a low or inefficacious range, and high or toxic range
There should be a method to address abnormal results	Several available doses or formulations available to allow dose adjustment

- To optimize plasma concentrations in patients infected with viruses exhibiting multi-class genotypic resistance, where experimental antiretroviral combinations and doses may be attempted in order to achieve maximum efficacy. This seems to be useful with the PI class, where increasing accumulation of resistance mutations results in moderate fold change in IC<sub>50</sub> which may be overcome in some cases by increasing the dose of the drug. However, this approach is complicated by toxicity arising from dose escalation and the increasingly restricted formulations of PI available make it difficult to make small dose adjustments.<sup>120</sup>
- Patients with medical conditions that may significantly alter the pharmacokinetics of a particular antiretroviral, such as hepatic or renal impairment, malabsorption or accelerated metabolism.

The value of TDM in monitoring adherence is questionable, as drug efficacy differs considerably depending on the pharmacokinetics of a drug (particularly the  $t_{1/2}$ ), the lower limit of detection (LLD) of the TDM assay (some LLD are still well above the IC<sub>95</sub>, therefore a patient may have sufficient plasma drug concentrations to achieve virological suppression but may show up as “undetectable” on a TDM assay) and the pattern of adherence (intermittent missed doses versus unstructured treatment interruptions).<sup>121</sup>

A major disadvantage to the use of TDM in HIV is that, for the majority of antiretroviral drugs, the trough concentration of specific antiretrovirals does not correlate with the extent of viral suppression (HIV RNA). Many drugs (such as NRTIs) undergo intracellular activation (and plasma concentrations of NRTIs correlate poorly with intracellular concentrations) or have antiviral activity that persists even with undetectable plasma concentrations (such as raltegravir).<sup>119</sup> This is further complicated by differing responses of resistant viruses to antiretroviral drugs, which is partly controlled for by the use of algorithms such as the inhibitory quotient (IQ), previously described.<sup>122,123</sup>

The large inter-patient variability in plasma concentrations of NNRTIs and PIs would suggest a role for TDM with use of these drug classes, however, there are no clear therapeutic cut-offs, with patients experiencing virological failures and toxicities at similar plasma concentrations.<sup>124</sup> Several studies have examined the role of TDM in clinical practice with inconsistent results. In the VIRADAPT study, in pre-treated patients treated with new HAART regimens, antiretroviral plasma concentrations strongly predicted the plasma HIV RNA decline.<sup>125</sup>

The ATHENA study randomized treatment-naïve, HIV-infected patients starting HAART containing either nelfinavir or indinavir to TDM with relevant dose adjustments or standard of care without TDM. At 12 months better treatment responses were observed in the TDM arm for both indinavir and nelfinavir, reflecting less virological failures in the nelfinavir group with TDM-guided optimization of drug levels, and less treatment-limiting toxicity with indinavir. However, this study was performed with un-boosted PI with formulations available enabling small-dose adjustments to be made. It is uncertain if a similar approach would be either feasible or beneficial with the boosted PI regimens now commonly used.<sup>126</sup>

The use of therapeutic drug monitoring as part of the post-marketing surveillance for drug safety to reveal unknown pharmacokinetic problems, such as unexpected drug-drug interactions or to identify populations with unexpected high or low concentrations, has proven to be of benefit as it has helped to define special circumstances where drugs such as the CCR5 antagonist maraviroc require dose adjustments in order to maintain efficacy.

### Summary

As the armamentarium of antiretrovirals increases, so too does the complexity arising from their varied and sometimes complex drug interactions. Maintaining awareness of these interactions will help preserve antiretroviral efficacy and aid in the goal of long-term suppression of HIV replication and restoration of normal life-spans in those affected. Further research into development of effective fixed-dose combinations will help simplify treatment further and should be a long-term goal in ongoing drug development internationally.

### Internet Resources

<http://www.europeanaidscouncilsociety.org/Guidelines/G1.htm>  
<http://www.iasusa.org/guidelines>  
<http://www.aidsinfo.nih.gov/guidelines>  
<http://www.hiv-druginteractions.org/>  
[http://www.bhiva.org/TreatmentofHIV1\\_2008.aspx](http://www.bhiva.org/TreatmentofHIV1_2008.aspx)  
<http://www.who.int/hiv/pub/guidelines/en/>  
<http://www.cdc.gov/hiv/resources/guidelines/index.htm>  
<http://aidsinfo.nih.gov/DrugsNew/Default.aspx?MenuItem= Drugs>

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# Surrogate Markers of Antiretroviral Efficacy

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## 69

### Introduction

The scale-up of antiretroviral therapy (ART) in low- and middle-income countries (LMIC) has been the largest public health undertaking to date. Access to treatment has improved dramatically in many high HIV burden countries. Data taken from cohorts in these countries have generally shown excellent outcomes with 2-year survival in the range of 60–90%.<sup>1,2</sup> These results are similar to those seen in high-income countries (HIC) apart from higher mortality during the first year of ART.<sup>3,4</sup>

The use of second-line regimens remains limited in LMIC.<sup>5,6</sup> This is likely to be because of a combination of under-diagnosis of treatment failure due to the limited sensitivity of current monitoring tools, limited access to second-line regimens, and a reluctance by treating clinicians to switch to second-line treatment, given the lack of access to subsequent treatment options. However, the number of people switching to second-line therapy will increase in coming years as access to virological monitoring and second-line agents increases and treated populations grow and mature. Second-line regimens remain three to twenty times more expensive than first-line regimens<sup>7</sup> and while price reductions have occurred, these have not been of the same magnitude seen with first-line agents. Increasing use of second-line regimens may therefore challenge the sustainability of ART programs and impact on programs' ability to continue to expand access to first-line therapy.

A key challenge for ART programs in LMIC is the appropriate use of efficacy monitoring technologies and ensuring appropriate use of second-line agents while containing the costs associated with monitoring. We outline here the key issues associated with the design of strategies to monitor the efficacy of ART in LMIC.

### Antiretroviral Efficacy Monitoring During First-Line Treatment in LMIC

The most sensitive test of antiretroviral efficacy is plasma HIV RNA, known as a “viral load” test. Despite the lack of randomized evidence of clinical benefit, treatment response is usually assessed

in HIC by 3–6 monthly measurement of plasma viral load. However, this test is relatively expensive and currently requires sophisticated laboratory infrastructure. Thus, this assay is not widely available in LMIC and is generally restricted to larger urban areas, particularly capital cities. In response to these financial and logistic constraints, alternative monitoring strategies are widely used. The World Health Organization (WHO) recommends that in settings where HIV viral load testing is not available, clinical and CD4+ T cell counting be used to detect treatment failure<sup>8</sup> as these measures are more feasible and more widely available.

### PERFORMANCE OF WHO CLINICAL AND CD4 CRITERIA FOR IDENTIFYING FAILURE OF FIRST-LINE ART

The most widely used non-virological surrogate markers of ART failure are those proposed by WHO. These include a single clinical criterion and three immunological criteria (Table 69.1). A number of studies have now documented consistently poor performance of these criteria for the diagnosis of treatment failure using a reference standard of HIV viral load with a range of clinically acceptable viral load thresholds (Table 69.2).<sup>9–12</sup> In particular, the sensitivity of these criteria is 20–33%, thus only approximately one in five to one in three individuals with virological failure is detected using these criteria. This leads to continuation of non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimens in the presence of ongoing viral replication, leading to accumulation of HIV drug resistance mutations, diminished efficacy of the current regimen, reduced potential activity of future regimens, immunological progression, and increased risk of clinical progression and death.

**Table 69.1:** WHO Clinical and Immunological Criteria for the Diagnosis of Antiretroviral Therapy Failure

New or recurrent WHO Clinical Stage 4 condition
Fall of CD4 count to baseline or below 50% fall from on-treatment peak value
Persistent CD4 levels below 100 cells/ $\mu$ L <sup>3</sup>

**Table 69.2:** Performance of WHO Clinical and Immunological Criteria to Identify Treatment Failure

Report	Setting	Reference standard	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Prevalence of virological failure (%)
An et al. (2007)*	Cambodia	VL >50	30	89	20	93	8
Chaiwarith et al. (2007)	Thailand	VL >50	20	86	12	91	9
Meya et al. (2007)	Uganda	VL >1000	31	87	16	94	8
Van Griensven et al. (2007)†	Rwanda	VL >40	27	82	17	89	12
Mee et al. (2008)	South Africa	VL >10,000	33	86	21	92	10

Abbreviation: VL: HIV viral load.

\*2003 WHO Criteria.

†2006 WHO Immunological Criteria.

The specificity and positive predictive value (PPV) of WHO-recommended clinical and CD4 criteria are also poor (Table 69.2). In published studies, the PPV ranges from 12% to 21% indicating that of those individuals designated under these criteria to be failing first-line ART, and therefore, potentially switched to expensive second-line regimens, only between one in five and one in eight are likely to be truly failing virologically. Thus the use of these criteria alone in determining the optimal timing of switch to second-line therapy is likely to result in significant inappropriate use of these expensive agents.

### ALTERNATIVE MONITORING CRITERIA

The relatively poor performance of WHO clinical and CD4 criteria for treatment failure has led to investigation of alternative non-virological criteria. Overall, attempts to identify alternative immunological criteria have been hampered by discordant immunological and virological responses to ART, i.e., the phenomenon where virological success is not matched with an increase in CD4 count, or vice versa. Thus where improvements in sensitivity have been identified, this has come at the cost of specificity and PPVs, with the latter generally remaining under 25%.<sup>10,11,13,14</sup> Another approach, for which some preliminary data exists, suggests possible benefit from adding simple laboratory or clinical markers such as “papular pruritic eruptions” to the existing WHO criteria,<sup>15,16</sup> but further work is required to define the potential benefit of this approach.

Investigators have also explored the potential role of adherence monitoring in the detection of treatment failure. Part of the rationale for this is that poor adherence is an “upstream” event that precedes virological failure, in contrast to detectable changes in CD4 counts, which are “downstream” effects that follow virological failure. Self-reported adherence has been the most widely used method for monitoring ART adherence and has been shown to be predictive of HIV viral rebound in some settings.<sup>17</sup> Furthermore, specific patterns of adherence, such as interruption of NNRTI-based treatment, has been shown to pose a greater risk of virological rebound than irregularly missed doses.<sup>18</sup>

An alternative to self-reported adherence is prescription- or pill-based adherence measures, referred to as pharmacy

adherence measures (PAMs). In a study conducted in southern Africa, these measures were superior to CD4 count criteria in predicting virological failure 6 and 12 months after initiating ART and adherence assessments performed prior to viral load and CD4 count assessments, were as accurate as CD4 count changes in predicting virological failure.<sup>19</sup> A study from Canada described PAMs predicting future viral rebound in an analysis of repeated measures of adherence that accounted for changes in adherence over time.<sup>20</sup> Additionally, US investigators have reported virological failure associated with poor “upstream” adherence assessments from electronic pill bottle caps (MEMS® [Aardex]). Poor adherence up to 90 days prior was associated with virological failure, suggesting there is sufficient time to implement adherence interventions that may improve virological outcomes.<sup>21</sup> Finally, a cross-sectional study in Nigeria described a combination of self-report adherence assessments and CD4 change criteria performing better than a WHO-based clinical and CD4 algorithm for detecting virological failure.<sup>22</sup>

If adherence monitoring is to be used to detect treatment failure, it is important to consider the relative qualities of alternative adherence-monitoring methods. Many methods to assess adherence, including unannounced pill counts, monitoring of ARV drug levels, electronic pill bottle caps (MEMS® [Aardex]) and web-connected pill boxes, are resource intensive and largely confined to research settings in both HICs and LMICs. Compared to self-reported adherence, which can be affected by recall or social desirability bias, PAMs are objective and may be calculated from routinely available medical and pharmacy records.<sup>23</sup> Furthermore, in studies reporting both self-report and PAMs, the pharmacy measure has been a more potent predictor of the virological outcome, whether it is virological suppression,<sup>24</sup> viral load change,<sup>25</sup> or virological failure.<sup>26–28</sup> Although PAMs have been consistently shown to predict virological failure in LMICs,<sup>26,28–30</sup> the data are limited by the variety of PAMs reported, including pill counts in clinic, “on-time” ART pick-up, and the amount of time a patient is in possession of a defined ART supply. Further studies that compare different types of PAMs, and define their relative advantages in comparison with adherence self-report, are needed to identify the best surrogate measures of virological failure.

## OUTCOMES OF NON-VIROLOGICAL MONITORING

Studies from LMIC have shown a high prevalence of resistance mutations at the time of treatment failure as defined by clinical and immunological criteria (Table 69.3).<sup>9,31</sup> In these studies the prevalence of resistance mutations would result in a very low likelihood of efficacy from first generation NNRTIs, and significantly diminished efficacy of nucleoside reverse transcriptase inhibitors (NRTIs) and second-generation NNRTIs.<sup>32</sup> Two studies have looked at the accumulation of resistance mutations in patients who were kept on a failing first-line regimen. Accumulation of resistant mutations occurred at a rate of 0.6 per 6 months to 1.6 per year of delay, and the additional mutations were mainly thymidine analogue mutations. A meta-analysis of published literature on resistance to first-line NRTI-NNRTI based highly active antiretroviral therapy compared cohorts with frequent viral load monitoring (at least 3-monthly) and no monitoring or infrequent monitoring (6 months or more). They found that patients coming from programs with no viral load monitoring have significantly more resistant mutations (NNRTI, M184V, and TAMs).<sup>33</sup> This study also suggested that at least 3-monthly viral load monitoring could reduce the accumulation of drug resistance mutations.

The clinical significance of delayed switching with non-virological monitoring remains to be clearly defined. In settings where there is an abundance of treatment options, virological failure does not always translate into a difference in clinical outcomes<sup>34</sup>; whereas, other studies have shown that delays in switching to a second-line regimen results in increased mortality when the failing regimen is a non-protease, inhibitor-based regimen.<sup>35</sup> In Côte d'Ivoire, with restricted access to second-line regimens, Seyler and colleagues showed that patients with a detectable viral load had an increased risk of immunological failure, but at 18 months there was no difference in morbidity between the patients who switched in time and those who remained on a failing regimen.<sup>36</sup> Emerging data regarding switch to second-line regimens have shown high mortality prior to switch and 10% mortality in the first year after switch,<sup>37</sup> but otherwise reassuring preliminary data with regard to the clinical and immunological efficacy of WHO-standard second-line regimens (boosted protease inhibitor-based) in programs

adopting non-virological approaches to monitoring of patients on ART is seen.<sup>37,38</sup>

## COMPARISONS OF VIROLOGICAL AND NON-VIROLOGICAL MONITORING STRATEGIES

Various approaches have been taken to investigate potential differences between virological and non-virological monitoring strategies. In a mathematic model based on outcome data from sub-Saharan African cohorts, viral-load monitoring in addition to CD4 and clinical monitoring did not have an impact on long-term survival in patients taking antiretroviral treatment.<sup>39</sup> Observational data from the ART-LINC cohort collaboration, based predominantly in sub-Saharan Africa, did not detect any increase in mortality in programs that had no viral-load monitoring; however, these data were drawn predominantly from the first year of ART during which time monitoring strategies are unlikely to have significant effect on clinical outcomes.<sup>3</sup>

Two randomized trials conducted in sub-Saharan Africa have compared alternative monitoring strategies. Unpublished adjusted analyses from the Home-Based AIDS Care study, conducted in rural Uganda, suggested that participants randomized to clinical and CD4 cell monitoring had a reduced risk of new AIDS-defining events or death when compared with clinical monitoring alone but viral load did not provide additional benefit to clinical criteria combined with CD4 counts.<sup>40</sup> However, these results should be interpreted with caution, given the study has never been published and the results of unadjusted analyses have not been made known. More recently, the results of the Development of Antiretroviral Therapy in Africa study were published.<sup>41</sup> In this large randomized trial of clinical monitoring versus clinical, CD4, and toxicity monitoring a significantly greater proportion of participants in the clinical monitoring arm suffered a WHO stage 4 event or death (event rate 6.94 vs. 5.24 per 100 person-years; Hazard Ratio 1.31 [1.14–1.51],  $P < 0.0001$ ). Neither arm included unblinded viral-load testing. A cost-effectiveness analysis based on these data suggested that CD4 cell monitoring is unlikely to be cost-effective unless used from the second year of treatment onwards and reagent costs were below US \$3.80. However, this analysis was based upon branded ART costs, and most participants were treated with a triple nucleoside regimen, limiting the generalizability of this threshold.

**Table 69.3:** Prevalence of Resistance Mutations in Patients Who Present with Immunological and Clinical Failure and Who Have a Detectable Viral Load Above 1000 copies/ml

	NNRTI (%)	M184V (%)	TAMS (%)	K65R/K70E (%)	Q151M (%)
Malawi (Hosseinipour 2009)	93	81	56	23	17
India (Kumarasamy 2009)	88	79	60	5	–

NNRTI: Non-nucleoside reverse transcriptase inhibitor.

## ALTERNATIVE APPROACHES TO THE USE OF VIRAL-LOAD TESTING

Despite the lack of clear evidence that virological monitoring is superior to non-virological monitoring, it remains evident that even with foreseeable improvements in the performance of non-virological criteria the majority of patients meeting these criteria will be false positive cases of virological failure. Given these test performance characteristics and current costs of viral-load testing and first- and second-line regimens many researchers have, therefore, recommended that where some viral testing is feasible,



confirmation of virological failure in individuals with suspected treatment failure using a viral load test should be implemented prior to switching to second-line treatment.<sup>42</sup> Indeed, a cost-effectiveness analysis has suggested viral-load testing to confirm suspected virological failure based on immunological and clinical criteria is highly cost-effective.<sup>43</sup>

Two potential forms of these “targeted” viral-load testing strategies exist. Firstly, current low-sensitivity non-virological criteria, such as those currently recommended by WHO, can be used for the initial evaluation. This strategy emphasizes the importance of reducing or eliminating false positives and inappropriate switching to second-line therapy.<sup>44,45</sup> Alternatively, a more sensitive “screening” set of non-virological criteria can be identified. This strategy effectively eliminates false positives, but also seeks to reduce false negatives. Prospective studies of this strategy are currently under way.

## Conclusion

Many barriers exist regarding optimal sequencing of HIV therapy in LMICs, including HIV efficacy monitoring. The need for HIV viral-load monitoring in LMICs remains controversial, but alternative monitoring tools based on clinical, immunological, and adherence measures have limited performance and lead to inappropriate and delayed switching. Viral load is therefore needed routinely or to confirm treatment failure before switching to second-line treatment. Nevertheless, many challenges to the widespread availability of HIV viral-load monitoring in LMICs remain, and addressing these issues will take concerted and systematic effort.

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## First Decade of ARV in Africa: Overcoming Barriers to Providing ARV Therapy in Resource-Limited Settings

Nathan Ford • Alexandra Calmy

### Introduction

The international effort to scale up antiretroviral therapy (ART) in the developing world that began in 2001 has been one of the most important programs in global health.<sup>1</sup>

Initially, however, there was a considerable resistance to providing ART in developing countries. Concerns were raised that ART was too expensive, too complex, and even that Africans could not adhere to lifelong treatment because they were unable to tell the time.<sup>2</sup> In particular, concerns were raised regarding the cost-effectiveness of ART compared to prevention interventions.<sup>3</sup>

Despite these concerns, within a decade, over six million people have been successfully started on and remain on therapy. This remarkable success in expanding access to ART was achieved by a global coalition of doctors, patients, civil society actors, governments, and non-governmental organizations, who refused to accept that millions of people in the developing world would be consigned to an early death from a disease that in the West had been transformed into a chronic, manageable condition, thanks to access to effective ART available since 1996.

This chapter provides an overview of the main policy and delivery challenges to the provision of effective ART in resource-limited settings: simplifying drug regimens and treatment monitoring; reducing the cost of medicines; overcoming human resource barriers; adapting the model of delivery; and integrating new evidence to improve the package of care.

### Global Advocacy to Reduce Treatment Cost

The early reluctance to support the provision of ART in developing countries was primarily driven by the cost of treatment. The fact that antiretroviral medicines were priced beyond the reach of the majority who needed them was an issue that had been on the international agenda for several decades: at the International AIDS Conference in Stockholm in 1988, there was a debate about how to ensure people in the developing world that they could access the treatment of that time, zidovudine monotherapy, which was marketed at a price of US\$8000 per year.<sup>4</sup> Triple therapy,

made available in late 1996, which revolutionized HIV/AIDS care in the West was considered far too expensive for resource-limited settings (particularly as it must be taken for life), UN agencies,<sup>5</sup> academics,<sup>3</sup> and major donors alike<sup>6</sup> all argued against providing treatment in favor of focusing funding on prevention. As a consequence, many high-prevalence countries still had no national treatment plan. South Africa, the country with the greatest number of people living with HIV in the world (some 5.6 million people at the time), only introduced a national HIV/AIDS treatment plan in November 2003.<sup>7</sup>

Civil society groups, and in particular people living with HIV/AIDS themselves, were critical to breaking the deadlock. Patient groups in Thailand, Brazil, South Africa, India, Kenya, Uganda, and other high-burden countries formed alliances with health providers, non-governmental organizations, and health groups in developed countries to argue the case that if the cost of treatment was too high, then it must come down.<sup>8</sup> Activist demonstrations took place from New York to Delhi to raise attention about the global inequities in access to treatment.<sup>9</sup>

In South Africa, home to the largest number of people living with HIV/AIDS, the government fought (and won) a court case against a consortium of 39 pharmaceutical companies over a law that would allow the government to source more affordable sources of antiretrovirals in neighboring countries.<sup>8</sup>

In Thailand, civil society groups began to raise legal challenges to patents in order to support the local production of affordable generic versions. In 2004, the Thai courts ruled that the patent on didanosine was unlawful because it lacked sufficient inventiveness on the part of the patent holder (didanosine was invented by researchers at the US National Institutes of Health and licensed to Bristol-Myers Squibb (BMS) in 1988; BMS extended patent protection through the addition of a common antacid buffer). In the final verdict, the Thai court states that “lack of access to medicines due to high-price prejudices the human rights of patients to proper medical treatment”.<sup>10</sup> This court ruling paved the way for the generic production of a number of key antiretroviral drugs.

The Brazilian government has, like Thailand, taken a strong position against the high price of medicines resulting from



the patent protection. Both countries have established public capacity to produce medicines, and in this way have been able to produce antiretroviral drugs at a fraction of the price demanded by multinational pharmaceutical companies. These two countries have played a leadership role among developing countries by challenging the international monopolies of antiretroviral drugs.<sup>11</sup> These programs paved the way for ART scale up in their countries by demonstrating efficacy and feasibility of large-scale access to ART via the public sector.

The global effort to scale up ART was only made possible from 2001, when an Indian generics manufacturer announced that they were able to manufacture triple therapy for less than a dollar a day. Other Indian generics companies made similar announcements, establishing a dynamic of global market competition that in 10 years has reduced the price of standard triple therapy from \$US 10,000 per patient/year to around \$US60.<sup>12</sup> Indian generics companies have played a critical role in supplying affordable generic versions of antiretrovirals to developing countries, providing over half of all antiretroviral medicines used in the developing world.<sup>13</sup>

The dramatic reduction on the cost of treatment was essential to shifting the cost-effectiveness equation, and from 2003 a number of international funding streams were established to support ART scale up, notably the Global Fund for AIDS, TB and Malaria and the US President's Emergency Plan for AIDS Relief.<sup>1</sup> Such dedicated funding for HIV/AIDS has been essential to scale up efforts.

## Overcoming the Human Resource Crisis

As programs began to enroll increasing numbers of patients, so it became rapidly clear that the lack of qualified health personnel, particularly in Africa, would prove to be a major bottleneck to increasing access to treatment. As soon as access to ART began to expand, public health experts began to raise attention about the human resource crisis in Africa as one of the most important limiting factors to widespread access.<sup>14</sup>

While in Western countries, HIV/AIDS has traditionally been managed as a specialized disease requiring a range of consultants from dermatology to oncology, health centers in sub-Saharan Africa faced with a dominant proportion of the global AIDS burden have a critical shortage of the most basic essential health staff. Countries like Malawi, where adult HIV prevalence is around 10%, have almost 100 times fewer doctors per population compared to the UK.<sup>15</sup> This crisis is partly driven by proactive recruitment of health personnel by developed countries, a practice that has been framed as an international crime.<sup>16</sup>

It therefore became apparent that a simplified treatment paradigm was required in resource-limited settings, entailing a shift from a specialized medical approach to a public health approach in which the majority of clinical tasks would be undertaken by lower health cadres such as nurses.<sup>17</sup>

Given the vast number of lives being lost to HIV/AIDS every day, such task-shifting strategies had to be employed outside of a formal evidence base, rather than waiting for randomized trial data to demonstrate that nurses could perform as well as doctors in

prescribing antiretrovirals; operational research was conducted to assess the effectiveness of such a strategy at the same time as it was being rolled out as a national policy, with countries like Lesotho,<sup>18</sup> South Africa,<sup>19</sup> and Malawi<sup>17</sup> all demonstrating that with adequate training and supervision, routine clinical management of patients on ART could be delegated to nurses. The effectiveness of this approach has since been confirmed by randomized trials.<sup>20</sup>

Substantial evidence has now accumulated around the effectiveness of different modalities of task shifting in contributing to improvements in service efficiency, increased access, sustained quality of care, and improved team dynamics.<sup>21</sup>

## Simplifying Drug Regimens and Monitoring

The delivery of ART at the primary care level required a treatment that is easy to store, simple to take, and could be administered by lesser trained health cadres via standardized guidelines. The development of fixed-dose combination ART was one answer to these requirements.

WHO guidelines for antiretroviral therapy in resource-limited settings, first issued in 2001, promoted the use of non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens as the preferred option.<sup>12</sup> This provided critical scientific and political support for the use of a simple, affordable twice-daily regimen.<sup>22</sup> Implementation at large scale began in 2003 and by 2008, access to antiretroviral drugs in low- and middle-income countries rose 10-fold.<sup>23</sup> As well as providing guidance on drug regimens, the WHO guidelines also addressed the need for simplified toxicity and efficacy monitoring: the ability to perform CD4 counts, viral load, and monitor levels of various markers of toxicity (alanine aminotransferase, lactate, and creatinine), while desirable, are not a precondition to starting treatment.

## Decentralizing HIV/AIDS Care to the Primary Care Level

Task shifting and simplification strategies have been essential to supporting equitable access to care. Doctors are in short supply and for the most part are located in hospitals in cities: rural parts of South Africa for example have 14 times fewer doctors than the national average<sup>19</sup> while over half of Mozambique's doctors are working in the capital city, Maputo.<sup>15</sup> Because of this uneven distribution of clinical staff, policies that insist on doctor-based provision of ART are, by default, policies that limit access to treatment for populations living in rural areas.

Patients who live far from healthcare services and have to travel long distances to access antiretrovirals have been found to have greater attrition and mortality rates compared to patients who leave closer to care. The cost and time required to travel to health centers have been associated with poorer adherence<sup>24</sup> and higher rates of defaulting from care.<sup>25</sup> The decentralization of antiretroviral care to health centers in rural areas is therefore essential to improving both access and equity.

Thus, another important adaptation to the standard model of HIV care practiced in the west has been the adaptation of

services such that ART could be delivered effectively at the primary care level by health center staff with supervision by clinical teams.<sup>18</sup> More recently, there has been a recognition that as the number of people on treatment continues to grow, so there will be a need to go even further in the decentralization of care and develop models of chronic disease care outside of the formal health system. In 2009, results from a cluster randomized trial done in Uganda found that home-based ART delivery was equivalent to facility-based ART delivery in terms of survival and virological suppression.<sup>26</sup> Similarly, a study in 2010 reported that in western Kenya, people living with HIV/AIDS have been trained to provide follow-up to clinically stable HIV patients in their communities and distribute ART and prophylaxis for opportunistic infections.<sup>27</sup> Such out-of-clinic approaches to ART management for stable patients will likely become increasingly important in the future as a strategy to decongest overburdened health services and simplify treatment delivery for patients.

### Improving Quality of Care

In the initial years of ART provision in Africa, HIV/AIDS was considered a humanitarian emergency, like floods and famines, and a rapid emergency response was required to reduce mortality as quickly as possible.<sup>28</sup> In order to provide effective and affordable care to the millions in need, adaptations to the western model of care were required to simplify treatment regimens and adjust delivery models to the realities of resource-limited settings.<sup>29</sup>

The need to continue to increase access to treatment for those not receiving it is still an urgent international priority. At the same time, however, there have been a number of important advances in terms of drug development and clinical science that need to be integrated into the package of care in the developing world. As developing country cohorts matured, so the limits of an emergency, public health approach for a chronic, lifelong condition became apparent.

Therefore, one of the most urgent challenges is to ensure that people are treated earlier in the course of their disease. The first step is to increase access to HIV tests and counseling; the second step is to link HIV testing with care. Finally, HIV treatment has to be started timely enough to avoid early mortality after treatment initiation.

In the earlier phases of ARV introduction in resource-limited settings, WHO recommended treating, by priority, the most severely ill patients, or patients with advanced immunosuppression (i.e.,  $<200$  CD4 cells/mm<sup>3</sup>). European and US guidelines recommended ART initiation at a CD4 cell threshold of 350 cells/mm<sup>3</sup> (moderate immunodeficiency), before severe immunosuppression occurs. This was originally based on concerns related to the accumulative risks of toxicity and drug resistance.<sup>30</sup> Such concerns have diminished in recent years as newer medicines have become available with fewer toxicities and better potency (reducing the chance of resistance development). The availability of these newer medicines, together with studies that have increased the understanding of the risks of developing life-threatening illnesses over time if ART is initiated at a low

CD4 count have shifted the risk-benefit equation.<sup>30</sup> Recent evidence from European cohorts shows that starting ART earlier (at least 350 cells/mm<sup>3</sup>) results in significant survival gains<sup>31</sup>; other cohorts analyses from the US even demonstrated a survival gain by treating even earlier, at 500 CD4 cells/mm<sup>3</sup>. The deleterious role of chronic, ongoing HIV replication is becoming clearer and thus the risk of non-HIV-related complications such as cardiovascular diseases and cancers can be reduced through earlier initiation of ART. As a result, US, French, and European guidelines have recently been revised and recognize that treatment can be initiated as early as 500 CD4 cells, especially in patients with other comorbidities, aged over 50, or with organ dysfunction.<sup>32</sup>

The need to provide ART earlier holds equally for resource-limited settings. Treatment guidelines issued by the International AIDS society in August 2008 state that “the core principle underlying these guidelines, namely pathogenesis-directed therapy with regimens designed to achieve full virologic suppression with minimal toxicity and maximal simplicity, is applicable to the developing world”<sup>33</sup> and the latest World Health Organization antiretroviral treatment guidelines for resource-limited settings released at the end of 2009 recommend a move towards earlier initiation at 350 cells/mm<sup>3</sup>.<sup>34</sup> As evidence emerges around the benefits of earlier treatment initiation in developing countries in terms of reduced mortality, morbidity, and hospitalization, so the challenge for donors and implementers will be to further adapt services in order to meet the increased demand.

Another challenge is to ensure access to some of the newer drugs with better efficacy and side-effect profiles that are brought to market. The standard treatment regimen in developing countries has relied on the drug stavudine. Reasons for choosing this drug include low cost (currently around US\$60 per person per year), availability as a fixed-dose combination that promotes adherence and simplifies drug supply management, excellent early tolerability, and its safety for use in pregnant women.<sup>12</sup> However, there are some severe side-effects associated with stavudine that have led its use to be progressively abandoned in developed countries.<sup>35</sup> In 2009, the World Health Organization revised its guidelines to recommend a move away from stavudine towards more drugs with a better safety profile, including tenofovir, which is also available as a once-daily regimen.<sup>36</sup> However, the relatively higher cost of this regimen has limited its inclusion in national protocols. Renewed advocacy efforts are needed to ensure that the price of tenofovir comes down, and that promising new drugs in the development pipeline are made accessible at an affordable price as soon as they become available.

### Looking Forward

Almost a decade ago, a common view among policy makers and donors was that ART was not an option for the developing world. At the same time as western countries were beginning to appreciate the major reductions in illness and death that ART could provide,<sup>37</sup> the provision of ART was argued to be too costly and too complex for developing countries,<sup>3</sup> and might even do harm to health services that were overburdened and under-resourced.<sup>38</sup>

Yet with three million people dying each year, mostly in Africa, withholding ART was considered simply unacceptable by a growing number of activists, academics, clinicians, and patients. Global inaction against HIV/AIDS was labeled as a crime against humanity.<sup>2</sup> A growing international movement fought against the high cost of treatment and in just a few years succeeded in reducing the price of ART to a fraction of its original price.<sup>8</sup> Small pilot programs that carefully selected a few dozen patients for treatment were rapidly swept away by demand and these pilot programs rapidly evolved into district wide programs treating thousands of people.<sup>39</sup> Treatment outcomes were evaluated and found to be as good as those reported in western settings.<sup>40</sup> The model of ART care was adapted from a resource-intensive individualized approach to a public health program that could be delivered by nurses at the clinic and community level.<sup>18</sup> Contrary to early fears, ART delivery was, after careful analysis, found to be supportive of health system strengthening.<sup>41</sup>

As coverage of ART has increased, so the broader benefits of ART are becoming apparent. In Malawi, adult mortality within the general population fell by a third as ART access increased<sup>42</sup>; similar declines in mortality have been reported elsewhere.<sup>43</sup> There is also emerging evidence to suggest that increased ART coverage may have an impact on prevention, by reducing the population-level viral load and thereby reducing the overall risk of transmission.<sup>44</sup> Mathematical models suggest that widespread ART coverage will result in a level of virological suppression at the population level that will reduce<sup>45</sup> or even eliminate<sup>46</sup> HIV transmission, and clinical trials are underway to assess the preventive impact of ART.<sup>47</sup>

Yet despite these major advances, it seems that most of the lessons of the last decade are rapidly being forgotten. In 2010, the high cost of treatment is again cited as a reason to accept sub-optimal care. The latest WHO guidelines recommend replacing older drugs long-abandoned in the west with more durable and less toxic alternatives, but because these newer drugs are more expensive, developing countries are reluctant to make the change.<sup>12</sup> Similarly, several studies have shown important benefits to starting treatment earlier, including one randomized trial which found that starting treatment earlier was associated with a four-fold decrease in mortality and a two-fold decrease in incident tuberculosis.<sup>48</sup> But lowering the threshold for initiation means that several million more people become eligible for ART, and while this may be clinically desirable, it is not politically supported at a time when many western donors are trying to get out of funding HIV/AIDS programs. As a result, just as the early benefits of ART were ignored in favor of cheaper interventions despite a clear mortality cost, this latest evidence is being swept aside by major funders who defend a policy of delaying treatment in order to ration resources.<sup>49</sup> International advisors are suggesting that treatment numbers should simply be frozen.

In 2005, the international community committed to a goal of achieving universal access to ART by 2010. Not only we have failed to achieve that goal but also the sustainability of gains made to date is under threat from multiple sides. Clinics are

reporting major stock ruptures of antiretrovirals due in part to insufficiencies in global fund financing.<sup>50</sup>

A decade ago, those in the international community who did not support the scale up of ART in Africa could argue that it was untested. In 2010, we know that treating HIV/AIDS on a large scale is entirely possible. We know that the price of treatment can be reduced; we know that simple, adapted models of delivery can support treatment provision even in highly under-resourced areas; and we know that major savings can be made by health systems that invest early. Improving the basic package of care can limit side-effects that delay the need for patients to switch to more expensive second-line regimens, while treating earlier will potentially yield massive public health benefits in terms of reduced transmission of HIV and other diseases.<sup>49</sup>

The challenge for the next decade is to increase access to treatment while at the same time ensuring that the package of care is continuously improved such that all patients—whether they happen to be born in the developed world or the developing world—can benefit from the latest improvements in drug development, clinical science, and public health.

### Summary

The last decade has seen remarkable progress in increasing access to ART in resource-limited settings. Early efforts to increase access to treatment were held back by concerns about the cost and complexity of providing ART, and fear of poor adherence leading to the development of drug resistance; however, these concerns were effectively overcome by a global coalition of health providers, activists, academics, and people living with HIV/AIDS who made the case that every effort must be made to overcome barriers to essential care when millions of lives depended on it. The high cost of treatment was reduced through advocacy efforts to promote access to generic drugs that reduced the global average cost of treatment to less than a dollar a day; the complexity of treatment was addressed through operational research to simplify treatment and monitoring protocols; the lack of human resources was overcome through task-shifting to support the provision of care by non-physicians and access was expanded through the development of models of care that could work at the primary care level. The challenge for the next decade is to increase access to treatment while at the same time ensuring that the package of care is continuously improved such that all patients can benefit from the latest improvements in drug development, clinical science, and public health.

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# Antiretroviral Drugs for HIV Prevention

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# 71

## Introduction

Currently, no high-efficacy vaccine against HIV exists; therefore, a range of other preventive measures, behavioral and biological, are the subjects of intense scrutiny.

Among prevention options, the use of antiretroviral (ARV) therapy has attracted considerable attention. ARV therapy is the mainstay of management for patients with established HIV infection. These drugs, by blocking critical steps in viral replication, prevent immune destruction and opportunistic infections. The same medications have now been considered for additional roles in preventing the transmission of the virus to people following (predominantly) sexual exposures.

Antibiotics and antiparasitic agents have long been used as part of preventative disease control, for example, in tuberculosis and malaria. Infection with HIV poses special problems, however, and even after 25 years since the discovery of the virus we have little understanding of the initial events in its natural history.

Development and efficacy testing of large number of potential microbicides and other preventive strategies, such as ARV pre- and post-exposure prophylaxis, have been hampered by the lack of simple animal models. Until recently, the only surrogate animal models used to study intravaginal or rectal HIV transmission were macaques infected with simian immunodeficiency virus (SIV) or SIV/HIV (SHIV) chimeric viruses, an expensive option. However, in the last few years, researchers have developed “humanized bone marrow-liver-thymus” mice that are susceptible to HIV infection; these models will be referred to later.

In this chapter, we review the uses of ARV for prevention, in the approximate chronological order that they have been investigated:

- Post-exposure prophylaxis following occupational exposure to HIV (PEP)
- Post-exposure prophylaxis following nonoccupational (sexual) exposure to HIV (nPEP)
- Pre-exposure prophylaxis for women with topical microbicides containing ARV
- Pre-exposure prophylaxis of HIV with oral ARV (PrEP)

- Effective treatment of infected persons to reduce HIV transmission to their partners
- Reduction of the HIV epidemic by widespread use of effective ARV in infected individuals (Test and Treat strategy)

## HIV Post-Exposure Prophylaxis

Post-exposure prophylaxis (PEP) is the use of ARV drugs to prevent HIV infection after high-risk exposure to HIV. Despite the widespread use of PEP in developed countries, the level of medical evidence for PEP remains relatively low. This section gives a general overview of the underlying principles surrounding PEP usage; practitioners should be familiar with national and local guidelines when prescribing PEP.

The rationale for PEP comes from a combination of animal models and retrospective case-control studies in healthcare workers and studies on mother-to-child HIV transmission. In the US, a nationwide, prospective, placebo-controlled trial of prophylaxis with zidovudine (AZT) after percutaneous exposure to HIV among healthcare workers had to be discontinued when only 84 subjects had enrolled after 1 year, since thousands would be needed to assess reduction of a 0.3% risk of transmission.<sup>1</sup> Therefore, there is no randomized clinical trial evidence attesting to the effectiveness or not of PEP.

Tenofovir given within 24 hours to macaques inoculated with simian immunodeficiency virus prevented infection in all animals but the failure rate reached 50% when given later. This animal model supports recommendations that PEP should be given as soon as possible and not later than 72 hours after exposure, preferably within 24 hours.<sup>2</sup> Animal models further support a 28-day course of treatment.<sup>2-4</sup> These early animal studies were imperfect because the HIV challenge was intravenous inoculation.

Evidence that PEP can prevent transmission of HIV in humans has been limited to a single case-control study of needle-stick injury (not sexual transmission) conducted by Cardo and colleagues.<sup>5</sup> From reports to national surveillance systems in the US, Italy, France, and the United Kingdom, 33 cases of HIV acquisition from 712 needle-

stick exposures were retrospectively identified. This study showed that persons who received AZT were 81% less likely to be infected with HIV than non-treated controls (95% CI, 48–94%).<sup>5</sup> The probability of HIV infection increased when blood was visible on the device, or a needle used in an artery or vein, after deep injuries, and the use of a large bore hollow needle. An AIDS-defining illness within the source was an additional risk of infection, probably reflecting the high viral load in advanced stages of HIV infection.<sup>5</sup> On the basis of this study, the Centers for Disease Control and Prevention (CDC) published guidelines in 1998 for PEP after occupational exposure; although, recommendations for non-occupational exposure (nPEP) were not published until 2005, due to paucity of evidence. An important factor often overlooked when transposing the Cardo study to non-occupational settings was that the majority of healthcare workers received PEP *within 4 hours* of their exposure.

Evidence that the prescription of ARV drugs may prevent human-to-human HIV transmission also came from studies investigating mother-to-child transmission. A number of studies proved that AZT when given to mothers during pregnancy and newborns for six weeks after birth reduces the risk of HIV transmission by 67%. This reduction is further improved if lamivudine (3TC) is used in addition to AZT. Furthermore, even if mothers were not treated but AZT was given to newborns, the risk of HIV transmission was 9% compared with 27% when no treatment was given (see other chapters).

From these studies, there is a crude estimate of approximately 70% reduction in HIV transmission risk by using a single ARV drug, a suggestion of a further 90–95% risk reduction if two drugs are used, and an estimate of the time frame (within 24 hours but still some effect out to 72 hours) within which any protective benefit might be achieved.

Nonetheless, it should be noted that PEP failures have been reported after occupational and sexual exposure even when PEP was initiated within the recommended time frame.<sup>6,7</sup>

However, there are still a number of critical areas where evidence is lacking:

**Duration:** PEP courses shorter than 28 days have not been studied.

**Number of drugs used:** Studies to date have looked at only one or two drug therapies. There is no evidence of any additional protection by using three-drug combinations.

**Choice of drugs:** To date, only AZT, 3TC, tenofovir, and nevirapine have been studied. Nevirapine is no longer recommended because of the risk of allergic reactions and hepatotoxicity. The use of reverse transcription inhibitors has theoretical appeal as they inhibit the generation of pro-viral DNA. On the other hand, protease inhibitors, which are active only after viral integration has occurred, do not prevent cellular infection and would be considered illogical choices for PEP.

## PEP FOR OCCUPATIONAL EXPOSURE

Accidental injuries with HIV-contaminated sharps in healthcare workers pose significant risk for HIV transmission; thus all cases

should be taken seriously and treated as an emergency. Usually the HIV status of source is known thus additional information about source viral load, current ARV treatment, and history of drug resistance may assist in determining an optimal PEP regimen. While high HIV RNA plasma viral load increases risk of infection it should be noted that undetectable viral load does not eliminate risk of infection.<sup>8</sup> There are many factors which may influence HIV transmission including different phenotypes and strain virulence. Every healthcare facility should have established procedures for needle-stick injury reporting and emergency response. The PEP initiation starter packs should be available to ensure that PEP, if indicated, is commenced without delays. Baseline HIV, Hepatitis B, and C serology should be obtained and appropriate follow-up arranged at week 4–6, month 3, and month 6.

## PEP AND COMMUNITY (“STREET”) NEEDLE-STICK INJURY

There are considerable media and community fears regarding risk of HIV infection after accidental percutaneous injury with injecting equipment discarded in public places, e.g., streets, parks, beaches, or children’s playgrounds. Despite common beliefs, the risk of HIV infection from this type of exposure is very low. HIV survival in discarded needles depends on temperature, humidity, viral load, and other factors. There have been no published reports about HIV acquired through “street” needle-stick injuries. Estimation of risk of transmission is based on HIV prevalence in injecting drug users (IDUs) which varies among communities. For instance, in Australia, prevalence of HIV among IDUs is low (1% = 0.01) and PEP is not prescribed for community needle-stick injury (risk =  $1/300 \times 0.01 = 1/30,000$ ). It should be noted that Hepatitis C and B are more prevalent and easier to transmit through community needle-stick injuries than HIV. Patients should be given Hepatitis B and tetanus immunization if not immune.

## PEP FOR NON-OCCUPATIONAL EXPOSURE (NPEP)

Unprotected vaginal and/or anal intercourse is the main reason for prescribing nPEP in non-occupational settings. Contrary to occupational settings, the HIV status of the source (partner) serostatus is often unknown, nor the exact time of exposure. Therefore, in clinical practice, it is necessary to estimate the risk of HIV transmission. Various epidemiological studies give an estimate of transmission risk associated with certain activities (Table 71.1).

Where nPEP guidelines have been produced, most recommend using nPEP for high-risk exposures (usually greater than 0.0001, or 0.000067 [otherwise expressed as 1/10,000 or 1/15,000]).

To estimate the risk, the following need to be determined:

- Route of exposure (vaginal/anal/oral, insertive/receptive)
- Knowledge of risk carried by route of exposure (Table 71.1)
- Risk of a source being HIV positive (calculated as prevalence of HIV in social group to which a source belongs (e.g., het-



**Table 71.1:** Exposure and Transmission Risk Per Single Exposure

Type of exposure with known HIV+ source	Estimated risk of HIV transmission per single exposure <sup>*(9–12)</sup>
Receptive anal intercourse	1/120 (0.008)
Receptive vaginal intercourse	1/1000+ (0.001)
Insertive anal or vaginal intercourse	1/1000+ (0.001)
Receptive fellatio with/without ejaculation	Not measurable†
Insertive fellatio	Not measurable†
Cunnilingus	Not measurable†
Sharing/use contaminated injecting equipment	1/150 (0.0067)
Occupational needle-stick injury	1/333 (0.003)
Community needle-stick injury	Not measurable†
Bites, etc.	Not measurable†
Other trauma	Not measurable†
Non-occupational exposure of intact mucous membrane§ and skin	Not measurable†

\*These estimates are based on prospective studies, not cross-sectional data or figures derived from modeling.

†This estimate has been rounded down from 1/909 to 1/1000.

‡Although there have been case reports of transmission, the risk associated with the exposure is so low that it is not measurable.

§Conjunctiva, oral, or nasal mucosa.

erosexual, men who have sex with men [MSM], sex worker, or IDU). Practitioners should be familiar with local seroprevalence data. Country-specific data for general population and some sub-groups is also available through the UNAIDS/WHO Global HIV/AIDS online database at [www.who.int/globalatlas/pgrms/HIV](http://www.who.int/globalatlas/pgrms/HIV).

- The presence of genital ulcerations or other sexually transmitted diseases which increase risk of HIV transmission

*Risk of HIV Transmission = Risk carried by route of exposure × risk of source being HIV+*

**Example 1:** Heterosexual male presents for nPEP following unprotected vaginal intercourse with a female sex worker while on holiday in Bali (Indonesia)

Risk = 0.0001 (or 1/1000) (risk of the single exposure via insertive vaginal intercourse) × 0.019 (or 1/10) (10% prevalence of HIV in female sex workers in Indonesia) = 0.0000019 (or 1/10,000); whether nPEP is recommended would be equivocal in this instance.

**Example 2:** Patient is a gay male who had unprotected receptive anal intercourse with a casual male partner in Sydney, Australia

Risk = 0.008 (or 1/120) × 0.01 (or 1/10) (10% prevalence of HIV in gay males in Sydney) = 0.00008 (or 1/1200); therefore, nPEP would be unequivocally recommended.

The following general guidelines should be considered when prescribing PEP, or nPEP:

- The usual duration of treatment is 28 days
- PEP is usually indicated within 72 hours of exposure

- Commonly used two-drug regimens include
  - AZT + lamivudine (Combivir): Some patients experience gastrointestinal (GI) side effects, thus often antiemetic, e.g., metoclopramide, is added.
    - Advantages: Lower cost.
    - Disadvantages: Twice a day, GI side effects are common.
  - Tenofovir + emtricitabine (Truvada)
    - Advantages: Once a day, less side effects.
    - Disadvantages: Higher cost
- Some guidelines recommend a 3-drug regimen, when a protease inhibitor is added, e.g., lopinavir/ritonavir (Kaletra). The rationale is that a 3-drug regimen is more efficacious than a 2-drug regimen for controlling HIV replication in chronically HIV infected patients, especially when the prevalence of drug resistance in the source patient population is high.<sup>13</sup> Despite this, there is no evidence that a 3-drug regimen is superior to a 2-drug regimen
- Avoid abacavir (potential life-threatening hypersensitivity) and nevirapine (fulminant liver failure requiring liver transplant has been recorded in a US healthcare worker).<sup>14</sup>
- The patient should be informed that ARV drugs are not licensed for PEP use and do not guarantee 100% protection
- Baseline HIV screening test at PEP presentation and follow-up visits at month 1, 3, and 6 should be arranged to detect those already infected with HIV or those who are seroconverting. nPEP recipients should be further screened for other sexually transmitted infections (STIs), including syphilis, Hepatitis B and C.

ARV drugs used for PEP/nPEP have significant toxicities. The most common are GI symptoms (nausea, vomiting), which result in almost half of PEP recipients prematurely terminating treatment due to unacceptable side effects.

nPEP should only be considered as one of the several methods of HIV prevention. From a public health perspective nPEP has been shown to have a limited contribution to the numbers of new HIV infections averted. An Australian retrospective study of 1552 nPEP recipients estimated that the number of new HIV infections prevented ranged between 0.9 and 9.2.<sup>15</sup> In the same six-year period there were 1,138 new infections reported in the geographical area covered by the study. A French study with 8958 individuals showed similar estimations (7.7 new infections prevented over a 4-year period).<sup>16</sup>

Several studies have found that nPEP is cost-effective when prescribed in high-risk settings (unprotected receptive anal intercourse with source being HIV+) as well as occupational exposures.<sup>16–18</sup> However, these studies assumed that provision of nPEP prevented lifetime costs associated with HIV infection. Such an assumption is true only if there are no ongoing exposure risks. Unfortunately, it has been shown that receipt of nPEP among the MSM population in Sydney was associated with a three-fold increased risk of subsequent HIV seroconversion due to continuing risk behaviors.<sup>19</sup>

There are some controversies around enhanced safe-sex messages, counseling, and health promotion to minimize risk of seroconversion when a patient presents for nPEP. In addition, there is uncertainty of how ARV therapy use within the source should affect the risk assessment. In HIV+ patients who are on therapy, those with an undetectable plasma viral load range from 75% in the U.S. to 95% in Australia.<sup>20,21</sup> Plasma viral load is certainly one of the strongest correlates of HIV transmission among serodiscordant couples. People with an undetectable plasma viral load have usually an undetectable viral load in semen.<sup>22,23</sup> Theoretically, if the source is known to be on ARV therapy (ART) with an undetectable viral load, then their risk of transmission would be negligible and nPEP would not be warranted. However, this situation has not been addressed with nPEP guidelines.

#### Keynotes:

- Inform patients that evidence that PEP prevents HIV infection is limited;
- Calculate risk of HIV transmission before prescribing PEP;
- Prescribe PEP for high-risk exposures (usually greater than 0.000067 [1/15,000]);
- There is no evidence that a two- or three-drug regimen is better than one drug; and
- ARV drugs with the best evidence are: AZT and tenofovir.

### PEP Guidelines (Online)

**WHO:** [www.who.int/hiv/pub/guidelines/PEP/en/](http://www.who.int/hiv/pub/guidelines/PEP/en/)

**UK:** [www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_088185](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_088185)

**USA:** [www.cdc.gov/mmwr/preview/mmwrhtml/rr5409a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5409a1.htm)

**Australia:** [www.ashm.org.au/default2.asp?active\\_page\\_id=251](http://www.ashm.org.au/default2.asp?active_page_id=251)

### Pre-exposure Prophylaxis for Women with Topical Microbicides Containing ARV

HIV prevention strategies that women can use and control remain a pressing priority. Microbicides are products that can be applied to the vagina (or rectum) with the intention of reducing the acquisition of STIs, including HIV. They are reviewed elsewhere in this volume (see Chapter 13, “Microbicides for Prevention of Sexually Transmitted Infections” by GP Talwar and Kavita B. Garg). However, three “first-generation” microbicides have already failed efficacy trials, and two-cellulose sulfate and nonoxonyl-9 actually increased women’s risk of infection.

Nevertheless, Abdool Karim at the Centre for the AIDS Program of Research in South Africa (CAPRISA), Durban, and her colleagues tested a 1% vaginal gel formulation of the ARV drug tenofovir between 2007 and 2009.<sup>24</sup>

The CAPRISA 004 trial assessed effectiveness and safety of a 1% vaginal gel formulation of tenofovir, a nucleotide reverse transcriptase inhibitor, for the prevention of HIV acquisition in women. A double-blind, randomized controlled trial was

conducted comparing tenofovir gel ( $n = 445$ ) with placebo gel ( $n = 444$ ) in sexually active, HIV uninfected 18- to 40-year-old women in urban and rural KwaZulu-Natal, South Africa. HIV serostatus, safety, sexual behavior, gel, and condom use were assessed at monthly follow-up visits for 30 months. HIV incidence in the tenofovir gel arm was 5.6 per 100 women-years, i.e., person time of study observation, (38/680.6 women-years) compared with 9.1 per 100 women-years (60/660.7 women years) in the placebo gel arm (incidence rate ratio = 0.61;  $p = 0.017$ ). In high adherers (gel adherence > 80%), HIV incidence was 54% lower ( $p = 0.025$ ) in the tenofovir gel arm. In intermediate adherers (gel adherence 50 to 80%) and low adherers (gel adherence < 50%) the HIV incidence reduction was 38% and 28%, respectively. Tenofovir gel reduced HIV acquisition by an estimated 39% overall, and by 54% in women with high gel adherence. No increase in overall adverse event rates was observed. There were no changes in viral load and no tenofovir resistance in HIV seroconvertors. A coitally related dosing strategy was selected to achieve high adherence, based on in-depth consultations with the communities involved. Sexual behavior data showed that women in the key study population had infrequent high-risk sex with migrant partners. Monkey challenge data and perinatal transmission studies informed the timing of doses in relation to sex. The “before and after” sex doses were modeled on the timing of nevirapine in its proven strategy for preventing mother-to-child HIV transmission. Women were requested to insert one dose of gel within 12 hours before sex and a second dose of gel as soon as possible within 12 hours after sex and no more than two doses of gel in a 24-hour period. Hence, the dosing strategy was referred to as “BAT24.” The latter restriction was imposed due to the lack of human safety data on more than two doses of gel per day. In addition, in CAPRISA, use of tenofovir gel reduced herpes simplex virus-2 incidence by 51% versus placebo, i.e., a “dual effect,” likely to be very important (unpublished data).

It is not possible to derive from this study any conclusions on the safety and effectiveness of tenofovir gel for anal sex. Similarly, it is not possible to make any conclusions on the effectiveness of tenofovir gel in relation to the timing of gel applications because when the gel was applied, BAT 24 was usually followed.

Another study, VOICE, which began enrolment in August 2009, will compare the safety, acceptability, and effectiveness of daily oral versus topical PrEP strategies in 5,000 women in South Africa, Uganda, Zimbabwe, and Zambia (NCT00705679). It will also be the first to provide comparative data on the 2 methods of administration.

### Pre-exposure Prophylaxis of HIV with Oral ARV

The earlier animal models<sup>2-4</sup> assessed efficacy of PEP after intravenous challenge with virus in macaques. In sexual transmission, HIV first replicates at a low level at the mucosal point of entry in the new host.<sup>25</sup> It is therefore possible that effective PrEP can exploit this brief period of virus vulnerability,

if founder populations of infected cells do not expand sufficiently to establish a self-propagating infection.

Recently researchers have created “humanized bone marrow-liver-thymus mice,” and shown that their female reproductive tract is not only susceptible to intravaginal infection by HIV-1, but can also be completely protected by PrEP with emtricitabine (FTC)/tenofovir (TDF).<sup>26</sup>

In addition, oral or subcutaneous PrEP with FTC, TDF, or both, has been shown to protect against rectal SHIV transmission in a rhesus macaque model that closely resembles human transmission.<sup>27,28</sup>

In humans, three clinical studies of oral PrEP have been completed to date. The first study<sup>29</sup> was conducted among women in Ghana, Nigeria, and Cameroon, and was intended as an efficacy study of oral tenofovir. Although the study was terminated early for political reasons, the data supported the safety of daily tenofovir. Another placebo-controlled safety study of once-daily oral tenofovir has recently been completed by CDC in 400 MSM, with a favorable result.<sup>30</sup>

Recently, Grant and colleagues,<sup>31</sup> reported that the combination of emtricitabine and tenofovir disoproxil fumarate (FTC-TDF) (Truvada), administered orally on a daily basis by men and transgender women (born male) who have sex with men, provides partial protection from HIV infection. The trial, called the Pre-exposure Prophylaxis Initiative (iPrEx) study, was a placebo-controlled, double-blind, randomized trial involving 2,499 subjects in the Americas, South Africa, and Thailand. Of the 100 incident infections, 64 occurred in the placebo group and 36 in the FTC-TDF group, for an estimated efficacy of 44% with a 95% confidence interval of 15 to 63. In the FTC-TDF group, the study drug was pharmacologically detected in 51% of subjects who remained free of HIV infection but in only 9% of those who became infected. Thus, exposure to FTC-TDF was associated with a reduction in HIV acquisition, which supports the biologic plausibility of the primary result. In fact, a small substudy found that risk of infection plummeted by 92% in people who had measurable drug levels in their blood.

The results of the Pre-exposure Prophylaxis Initiative study also reveal real challenges and raised many concerns.<sup>32,33</sup> First, the association between self-reported drug adherence and pharmacological detection of the study drug was very poor, which underscores the need for better reporting tools to predict drug adherence. Second, although renal insufficiency and decreases in bone mineral density were seen in a relatively small fraction of subjects and was reversible on drug discontinuation, this finding raises both safety and monitoring concerns regarding possibly cumulative toxic effects associated with large-scale exposure of at-risk persons to daily FTC-TDF therapy for an extended period. The side effect profile for FTC-TDF was probably diluted, given the reported medication-compliance issues, and thus would probably be more substantial with full compliance. The study also raises cost-effectiveness concerns, in that 1,220 subjects were prescribed medication for up to 2.8 years in order to prevent an estimated 28 infections, or expressed another way; treating 43

people to stop one infection. Furthermore, the fact that FTC-TDF (Truvada) is patent-protected, and therefore an expensive medication, raises questions as to whether its use as a preventative measure should be funded by the government, private health industry, or by the individual. It should be noted that this study was conducted in highly supportive environment when specific high-risk groups had access to counselling (safe sex) and health-promotion activities (condom use) which may be not a case in real-world settings, different populations and geographical locations. There is concern that the widespread use of PrEP might lead people to take more risks than they would otherwise, offsetting the benefit of the intervention. There is always a risk for evolution of multi-drug resistant HIV strains.

Other studies of PrEP are ongoing, in IDU (Bangkok), women in Africa (VOICE-see earlier section on microbicides), and FEMPrEP, (a phase III trial to evaluate the safety and effectiveness of daily oral TDF/FTC), all of whose results should further guide recommendations in this field.

There are currently no guidelines for prescribing PrEP, although, CDC has published interim guidance.<sup>34</sup>

## Effective Treatment of Infected Persons to Reduce HIV Transmission to Their Partners

Viral load is the major determinant governing the risk of sexual transmission in HIV-1 discordant couples,<sup>35</sup> and therefore, effective ARV should dramatically reduce transmission rates. In a meta-analysis of data from five studies, some of which were unpublished, investigators reported only five cases of HIV-1 transmission from patients receiving ART to sexual partners during 1098 person-years of follow-up, which is consistent with an infection rate of 0.19–1.09 per 100 person years.<sup>36</sup>

In 2010, Donnell and colleagues (the Partners in Prevention HSV/HIV Transmission study team)<sup>37,38</sup> reported the results of a study nested within a placebo-controlled trial, which showed no effect of Herpes simplex virus-2 treatment on HIV transmission in nearly 3,400 African serodiscordant heterosexual couples. As one in 10 participants started on ARV during the trial, the investigators were able to compare HIV transmission before and after starting treatment. HIV incidence was 2.24 per 100 person-years before starting ARV (102 transmission events) and 0.37 per 100 person-years after starting treatment (one event which probably occurred before full suppression of viral load in the index partner), yielding an adjusted incidence rate ratio of 0.08, a 12-fold reduction in transmission.

Investigators in Switzerland also reviewed transmission rates among discordant couples in their country, concluding that in a monogamous relationship, with no concurrent sexually transmitted infections, the risk of HIV transmission was “negligible.”<sup>39</sup> Another observational cohort study from Uganda reported similar data. Free ARV programs were initiated in 2004, and the rates of HIV-1 transmission before and after the programs began, in the Rakai district, were measured.<sup>40</sup> Two hundred and fifty HIV-1 discordant couples were followed between 2004 and



2009 and 32 HIV-1-positive partners initiated ART. Forty-two HIV-1 transmissions occurred over 459.4 person-years prior to ART initiation, incidence 9.2/100 person-years (95% CI, 6.59–12.36). In 32 couples in which the HIV-1 index partners started ART, no HIV-1 transmissions occurred during 53.6 person-years. The 95% confidence interval for the incidence rate difference was -11.91 to -6.38 ( $p < 0.0097$ ). Couples reported more consistent condom use during ART, but there was no significant difference in the number of sexual partners or other risk behaviors. Although there was a significant increase in consistent condom use following ART initiation, the reduction in risk was most likely due to the direct reduction in HIV-1 viral load in the HIV-1-positive partners on ART. These findings add to the growing body of evidence supporting the use of ART for HIV-1 prevention.

Ongoing studies such as the HIV-1 Prevention Trials Network 052 study (by NIAID) will test the hypothesis that ART can prevent HIV-1 transmission among HIV-1 discordant couples by randomizing couples in whom the infected partner has a CD4 cell count of 250–550 cells per microliter to either start ARVs immediately, or wait until the CD4 count drops below 250 cells per microliter<sup>41</sup>; results are expected in 2014. This trial will provide useful data on long-term measures of efficacy of ART among discordant couples, adherence when ARV are initiated earlier, incidence of drug resistance, and potential risk compensation.

### Reduction of the HIV Epidemic by Widespread Use of Effective ARV in Infected Individuals

The “treatment as prevention” strategy aims to reduce community viral load and assumes that this will reduce HIV transmission. Indeed, lower rates of HIV diagnosis in San Francisco and British Columbia have accompanied lower viral loads in HIV-infected people undergoing viral tests,<sup>42,43</sup> and in Taiwan, rapid expansion of ARV was associated with a 50% reduction in new HIV diagnoses.<sup>44</sup> Granich and colleagues<sup>45</sup> have developed a statistical model predicting that universal testing of all sexually active adults and immediate ARV therapy (regardless of CD4 count) could have a major effect on generalized epidemics.

However, Hosein and Wilson<sup>46</sup> make pertinent comments on the situation among MSM in France, with continuing high incidence,<sup>47</sup> despite high uptake of highly active antiretroviral therapy, and where 92% of treated patients achieve an undetectable viral load. Similar situations pertain among MSM in Sydney<sup>19,48</sup> and in Amsterdam.<sup>49</sup> They suggest that the preventative role of treatment may be different in MSM to heterosexuals and IDU, because of higher biological transmission rates, and the sexual milieu of MSMs. As mentioned in the French study, such circumstances include a high HIV prevalence, increased rates of unprotected anal sex with more partners, and increased prevalence of STIs.

Thus, merely intensifying a treatment uptake as prevention strategy for MSM without addressing other co-existing issues at the

individual or community level may not lead to sustained changes in some HIV epidemics. As the majority of HIV transmissions worldwide occur within the heterosexual community, selective use of ARV medications may have differing outcomes on HIV transmission in different populations, e.g., in countries where transmitted drug resistance is common, where sub-optimal first-line ARV use has created a pool of resistance to these agents, or where ARV roll-out has not reached the majority of infected people.

### Conclusions

ARV drugs alone, while having a dramatic impact at the individual level, are unlikely to have a significant impact on HIV transmission at the population level unless accompanied by a range of additional strategies, such as, universal access to testing and treatment, education on risk behaviors, and removing barriers to condom use and needle/syringe exchange programs. All of these strategies unfortunately highlight deficiencies in the way health and HIV is managed globally. The greatest challenge in reducing HIV transmission rates is not necessarily achieved through biological interventions such as ARV alone but the more difficult task of changing human behavior.

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## Introduction

The first case of primary HIV infection was described in 1984 in a nurse from the UK who had received an accidental needle-stick injury.<sup>1</sup> The HIV can also be transmitted to humans via unprotected sexual intercourse with an infected individual, transfusion of infected blood, injection drug use with contaminated needles and syringes, or from infected mother to the child at the time of child birth or breast feeding. The amount of HIV in the blood gets very high within a few days or weeks after HIV infection. Some people get a flu-like illness. This first stage of HIV disease is called “acute HIV infection” or “primary HIV infection.” Our understanding of the pathophysiology of primary HIV infection and the clinical signs and symptoms has advanced considerably in the years following this initial case. A better understanding of the events surrounding primary HIV infection may contribute to vaccine development, clinical treatment, and improved strategies to prevent transmission. This chapter will focus on the pathophysiology, clinical presentation, diagnosis, and treatment of primary HIV-1 infection, and HIV is used in the whole chapter to refer HIV-1.

## Pathophysiology

Despite the importance of pathophysiologic events surrounding primary HIV infection, data are limited from human studies. The majority of studies have been performed in rhesus macaques, experimentally infected with the monkey equivalent of HIV, simian immunodeficiency virus (SIV). These studies have revealed that after endocervical exposure, only a small number of infected cells were detected in the first three days close to the site of exposure. T cells in the lamina propria represented the predominant cell population at this early stage.<sup>2</sup> The majority of the HIV transmissions worldwide occur across a mucosal surface such as the anorectal mucosa, vaginal mucosa and, less frequently, the oral mucosa.<sup>3,4</sup> HIV-receptive cells have been found in the lamina propria of rectal, cervicovaginal, foreskin, urethral, and oral epithelia in primate models.<sup>5</sup> Indeed, certain characteristics of the mucosal compartment render it extremely permissive to

HIV-1 infection and supportive of HIV-1 replication. Compared with circulating lymphocytes, a greater percentage of mucosal cells express the CCR5 chemokine coreceptor.<sup>6,7</sup> The study of the human gastrointestinal (GI) tract during acute HIV-1 infection is challenging. Consequently, initial work in this area emerged from the SIV-macaque model. A striking depletion of intestinal CD4+ T cells was noted in macaques within days of SIV infection, at a time when little or no CD4+ T cell depletion was evident in the peripheral blood or lymph nodes.<sup>8</sup> Furthermore, intestinal CD4+ T cell depletion occurred regardless of whether viral inoculum was intrarectally or intravenously delivered.<sup>8</sup> These studies were subsequently extended to demonstrate that GI lymphocyte depletion occurs in all stages of SIV.<sup>9</sup> Studies by Mattapallil and colleagues<sup>10</sup> and Li and coworkers,<sup>11</sup> demonstrate rapid infection and destruction of GI memory CD4+ T cells within days of infection with SIV. In recent studies on humans, it has been demonstrated that during acute HIV-1 infection, a preferential and profound depletion of CD4+ T cells occurs within the GI tract.<sup>12–14</sup> Over the subsequent days, the infection spreads to other cell types, including dendritic cells (DCs) and macrophages, with the majority of infected cells represented by resting CD4+ T cells. Resting T cells constitute a significant reservoir of latent HIV that may be activated to complete the replication cycle upon activation of the host cell. It has been shown *in vivo* that HIV can infect T cells that are not fully activated. During the course of HIV infection, integrated and replicative-competent provirus can be found in a population of resting memory CD4+ T cells (1,2) and the frequency of these cells tends to remain stable for years, decreasing only minimally with the administration of combination antiretroviral therapies.<sup>15,16</sup> DCs are believed to play a key role in the dissemination of HIV following local infection. DCs provide a highly specialized function whereby HIV antigens encountered in peripheral tissues can be brought into contact with T cells in draining lymph nodes and ultimately generate an immune response to these antigens. HIV is capable of entering immature DCs at the epithelial and mucosal surfaces and undergoes limited replication until DCs encounter T cells in lymphoid tissues.<sup>17</sup> In addition to their



role in antigen presentation, DCs may be capable of facilitating the spread of HIV through the unique lectin called DC-SIGN. When bound to DC-SIGN, HIV can remain viable for days potentially providing an additional mechanism for transport to the regional lymph nodes.<sup>18</sup>

Following the initial sequence of events, systemic dissemination occurs, with HIV-1 being culturable from plasma within five days of initial infection.<sup>19</sup> In animal models productive infection in cervicovaginal tissues and hematological dissemination is followed by systemic infection between six and 10 days with peak viral infection in other tissues. Estimates in humans of the incubation time from mucosal infection to initial viremia range from 4 to 11 days.<sup>20</sup> After initial infection, a rapid rise in plasma viremia ensues with dissemination of the virus to lymphoid organs and trapping of virus by follicular DCs.<sup>21–23</sup> This stage of infection may be particularly important from a public health perspective, as it is likely to be accompanied by high levels of replicating virus, and consequently, high infectivity among individuals who may not be aware of their infection status.<sup>24</sup> Sexual transmission of HIV-1 may be enhanced at this stage by breaks in the genital mucosa and increased inflammation due to the presence of genital ulcer disease, urethritis, or cervicitis.<sup>25</sup>

Transmitted HIV-1 viruses are typically macrophage-tropic and lack the ability to form multinucleated syncytia in tissue culture.<sup>26,27</sup> Virus entry requires the binding of glycoprotein 120 to the CD4 molecule on susceptible cells in conjunction with binding to the coreceptor for macrophage-tropic strains, CCR5.<sup>28,29</sup> The binding of CD4 to gp120 results in a structural change, which exposes a coreceptor binding site. Following coreceptor binding, further structural rearrangements occur, predominantly in gp41, which are thought to be sufficient to facilitate viral fusion and cell entry. The ability of HIV to vary the conformational structure of the envelope protein and coreceptor may play a role in immune evasion by the HIV. T cell-tropic strains of HIV-1 seen in acute but predominantly in chronic infection require the coreceptor CXCR4 for entry.<sup>30</sup> These different strains of the HIV-1 are now referred to as R5 and X4 viruses, respectively.<sup>31</sup> Individuals who are homozygous for a 32-bp deletion in CCR5 (CCR5Δ32) are relatively resistant to infection with R5 strains of HIV-1.<sup>32,33</sup> Rare cases of transmission of X4 viruses have been reported in individuals homozygous for CCR5Δ32.<sup>34,35</sup>

Following the establishment of HIV-1 infection in the lymphoid tissues, peak viremia occurs an average of six to 15 days after the onset of symptoms, with viral load levels in the range of one to 70 million copies/ml.<sup>36,37</sup> Over the following weeks, the viral load falls by several orders of magnitude despite the absence of neutralizing antibody.<sup>38</sup> The early control of HIV replication at this stage is believed to be largely due to the cellular immune response to the virus.<sup>39</sup> A temporal relationship has been shown in humans between the appearance of HIV-1 specific cytotoxic T lymphocytes (CTLs) and declining viral load.<sup>40,41</sup> Data from Indian patients infected with subtype C virus suggest that patients exhibiting consistent subtype-specific T cell responses to

HIV-1 gag might have better control of viral replication in early HIV infection.<sup>42</sup> Many of the clinical symptoms observed during primary infection may reflect the immune response to the virus with the ultimate resolution of symptoms coincident with the decrease in plasma viral load.<sup>43</sup> After the fall in plasma viral load, a viral set point is established normally around 12 to 18 months after infection.<sup>44</sup> The absolute level of the viral set point and early viral trajectory have been correlated with the duration of AIDS-free survival time.<sup>44,45</sup>

Numerous studies among patients infected with subtype B virus have suggested that the rate of clinical progression to AIDS following initial infection may depend upon early immunologic and virologic events occurring soon after primary HIV infection.<sup>45–47</sup> A recent study of subtype C infected seroconverters from India suggests that the pattern of disease progression may be different in the Indian setting. The authors found that the viral set point reached following infection was similar among Indian patients to that seen in the North American setting but the median trajectory of increasing viral load in Indian seroconverters was greater than what has been reported in untreated seroconverters from the US.<sup>48</sup> This discrepancy may be explained by a number of factors. Low socioeconomic status and limited access to healthcare has been associated with a worse survival among HIV-infected patients in Canada and the UK.<sup>49,50</sup> Other factors, such as the high rate of endemic diseases like tuberculosis, and parasitic diseases may be a factor in the altered disease progression observed among Indian seroconverters.<sup>51–54</sup> Additional host factors which may affect disease progression in resource poor setting include the level of immune activation in the population and the presence of micronutrient deficiencies.<sup>55–57</sup>

## Clinical Presentation

If present, the signs and symptoms of primary HIV infection usually appear within days to weeks following exposure.<sup>58</sup> The primary HIV syndrome may last from a few days to more than 10 weeks with the majority of individuals experiencing symptoms for less than 14 days.<sup>59</sup> The three most common presenting symptoms include fever, fatigue, and rash.<sup>59</sup> Other reported symptoms include headache, myalgia, pharyngitis, nausea, vomiting, diarrhea, and night sweats.<sup>60</sup> A maculopapular skin rash seen in primary HIV infection usually involving the face, trunk, and limbs, which may also involve palms and soles, is helpful in making the diagnosis. Primary HIV disease may rarely present with genital ulcers.<sup>61</sup> Important clinical manifestations of acute HIV infection are summarized in Table 72.1.

The non-specific constellation of symptoms associated with primary HIV infection presents a diagnostic challenge to healthcare providers.

Many of the studies investigating the signs and symptoms of primary HIV infection have relied on the referral of symptomatic high-risk persons resulting in an important element of detection bias. A nested case-control study examining the clinical signs of primary HIV infection among Indian patients revealed fever, joint

**Table 72.1:** Common Symptoms Associated With Acute HIV Syndrome

Symptomatic symptoms	50–90%
Fever	96%
Adenopathy	74%
Pharyngitis	70%
Morbilliform, maculopapular rash	70%
Diarrhea	32%
Headache	30%
Nausea/vomiting, neurological, e.g. aseptic meningitis	27%
Genital ulcers	10%
	Rare

Adapted from The 2002 Abbreviated Guide to Medical Management of HIV Infection.

pains, night sweats, and inguinal adenopathy to be significantly associated with p24 antigenemia.<sup>62</sup> Of the 58 subjects with recent HIV infection, 27 (47%) reported fever, joint pains, and/or night sweats. A rash, which has been proposed as an important clinical sign in many of the earlier studies, was only found in 2 (3.5%) subjects in this study. The high rate of symptoms observed among the control patients in this study made it difficult to distinguish those with acute HIV infection from other clinic patients. In the uncommon occurrence of genital ulcers in PHI, herpes simplex virus infection should be considered in differential diagnosis. Syphilis should also be excluded especially in areas where it is prevalent. A recent cohort study from Uganda found that only a minority of subjects experienced a seroconversion illness (five of 27 or 18.5%), which was similar to the rate observed among control subjects (four of 22 or 18.2%).<sup>63</sup> The authors attribute the lack of seroconversion illness to the possible immunological differences in the responses to HIV-1 infection in African populations and also the high background rate of other illnesses like malaria which make it difficult to distinguish the seroconversion illness from other illnesses. The non-specific nature of symptoms surrounding primary HIV infection and the high rate of other infectious diseases, which may mimic the seroconversion illness, make it prudent to include primary HIV infection in the differential diagnosis of any patient presenting with a non-specific flu-like illness and recent high-risk behavior. An accurate history of exposure risk is also an essential tool in identifying individuals at risk for primary HIV infection who may not experience any symptoms suggestive of a seroconversion illness. Unfortunately, diagnosis of acute HIV infection is an uncommon event, and the advantages of such early diagnosis are not always apparent to the patient or even to the provider. Understanding the association between symptoms, initial HIV viremia, and ultimate viral set point may help determine treatment decisions for such patients. The incubation period and duration of acute retroviral syndrome have been associated with progression to AIDS.<sup>64</sup>

## Diagnosis

Recognizing primary HIV infection has important implications for controlling the spread of the epidemic. It has important clinical and public health implications. The acute infection may be the only opportunity to diagnose HIV before the patient

presents with AIDS-defining conditions. It also allows for early treatment intervention if warranted or to enroll the patients into therapeutic studies. However, more emphasis has been put on the infectiousness in early infection. The early stages of HIV are particularly important due to the high viral load in blood and genital secretions and lack of awareness of infection characteristic of this period.<sup>65</sup> Two studies have examined this period in mathematical models of transmission and have found that the primary stage has an infectivity rate much higher (50–100 fold) than subsequent periods following infection.<sup>66,67</sup>

The laboratory diagnosis of primary HIV infection can be made by the demonstration of a positive virologic test in the absence of HIV-specific antibodies. The detection of p24 antigen in serum or plasma has been recommended for the diagnosis of primary HIV infection during the seroconversion window period and has been shown to be 88.7% sensitive and 100% specific in one cohort study.<sup>68</sup> HIV RNA assays have been shown to have a sensitivity of 100% and specificity of 97%, but their application to the diagnosis of primary HIV infection is limited by their feasibility, cost, and potential for false positive results making confirmatory testing necessary.<sup>69</sup> False positive results may be limited by the use of repeat testing and imposing a threshold of greater than 2000 copies/ml.<sup>70</sup> To reduce the cost of HIV RNA assays in the diagnosis of acute HIV infection, the use of pooled specimens was considered in a low prevalence, high-volume clinic setting. This testing strategy identified approximately 10% additional infections compared with the conventional HIV antibody testing strategy, and may offer an improved algorithm for identification of primary HIV infection in low-prevalence settings with high volume laboratory testing.<sup>71</sup> The current cost and pros and cons of various options for patients in developing countries are summarized in Table 72.2.

The most recent tool which has become available to identify individuals recently infected with HIV-1 has been the use of the sensitive/less-sensitive (detuned) enzyme immune assay strategy.<sup>72</sup> This strategy has been shown to distinguish recent from chronic HIV-1 infection among individuals with subtype B infection but only after seroconversion has occurred, limiting its application.

**Table 72.2:** Testing Options and Costs in Developing Countries

Test	Approximate cost (excluding labor), US\$	Advantages	Disadvantages
EIA*	5	Inexpensive, simple	Not useful for primary infection
p24	25	Simple	Moderately expensive
RT-PCR Pooled	100	Sensitive	Technologically complex, False positives, requires confirmation
PCR	20	Low cost, sensitive	Cost increases in high prevalence populations, requires confirmation

\*Free under national program of many countries.

The detuned enzyme immune assay is currently under evaluation in other settings where diverse subtypes are transmitted and may provide a useful tool in future for the diagnosis of early HIV infection in patients who are already HIV-antibody positive.

Despite the importance of recognizing and diagnosing primary HIV infection, mandatory testing for HIV has been discouraged by a number of authorities including the American Medical Association.<sup>73</sup> Mandatory testing of certain at risk groups such as pregnant women could result in an avoidance of care with the ultimate result of increasing HIV transmission. However, introduction of routine testing of all pregnant women (through counseling and informed consent) under the Prevention of Parent to Child Transmission program of National AIDS Control Organisation in India has started showing its positive effects with the drop in mother-to-child transmission rates. Numerous reports have highlighted the success of voluntary counseling and testing programs in diagnosing HIV infection with the adoption of these programs by the majority of healthcare policy makers.<sup>74,75</sup>

## Treatment

The period following initial infection with HIV is characterized by a high viral load, rapid virus turnover, and widespread dissemination.<sup>36,76</sup> The most homogeneous virus population in the setting of a mostly intact immune system also characterizes this period. It would appear that this time period would represent an opportunity to preserve the immune system, and attack the virus with the most effective antiviral pressure. It is unclear whether antiretroviral therapy should be initiated at PHI and for what duration of time. The Spartak study will elucidate whether a short period of ART initiated at primary HIV infection will delay the time to CD4 T cell count below 350 cells. Some early reports have been encouraging and supportive of this view showing that patients treated early in infection can recover or retain HIV-specific CD4+ T cell responses and also maintain an effective CD8+ T cell response.<sup>77,78</sup> However, concern has been raised by some investigators that early initiation of therapy does not allow for the immune system to generate a full response to HIV antigens.<sup>79,80</sup> The breadth and magnitude of CTL responses was less in those treated before seroconversion, but the viral diversity was also significantly less in this group compared to those treated after seroconversion. The authors of this study concluded that early treatment resulted in a more narrowly directed CTL response with stronger T helper cell responses resulting in a less diverse virus population. A subsequent study of a large seroconverter cohort in Australia found that early antiretroviral treatment of primary HIV infection resulted in better early virologic responses but no significant difference in immunologic responses (based on changes in CD4+ cell count).<sup>81</sup> Although these early reports are encouraging, more research is needed into the long-term benefits of early treatment before any clinical recommendations can be made. Theoretical advantages supporting early treatment include the potential to decrease the

severity of acute disease, the potential to alter the viral set point and ultimately alter the rate of disease progression, reduce the rate of viral mutation, preserve immune function, and possibly reduce the risk of HIV transmission. These theoretical benefits are balanced by the potential risks of therapy, which include drug toxicity, cost, side effects, adverse effects on quality of life, potential early development of drug resistance, and the burden of long-term therapy. Currently in the North American setting, routine highly active antiretroviral therapy (HAART) treatment of patients with acute HIV infection is not recommended. It is recommended that individuals found to be acutely infected with HIV be referred to specialists for possible enrolment in early treatment studies.

Considerable interest has been generated in recent years to the potential for structured treatment interruption of HAART in the primary HIV infection period to facilitate the autoimmunization of infected individuals with the goal of maintaining viral suppression in the absence of HAART. Eight patients from Boston were treated with a structured treatment interruption regimen and were able to maintain viral suppression in the absence of drug therapy.<sup>82</sup> Additional studies in macaques acutely infected with SIV illustrated that intermittent interruption of therapy is the factor responsible for boosting immunity.<sup>83</sup> Subsequent early reports from human trials have been less encouraging with spontaneous control of viremia observed in only one-third of cases after four cycles of two months off therapy.<sup>84</sup> Currently, clinical trials of structured treatment interruption are ongoing to assess the benefit of this new approach to the management of primary HIV infection. The outcomes from these studies will be required before any recommendations regarding this approach to therapy can be made.

## Conclusion

Acute infection caused by HIV gradually destroys the immune system. Primary HIV infection represents a period of rapid change in virologic and immunologic parameters. This magnitude of change is often not translated into a recognizable clinical syndrome creating a diagnostic challenge for healthcare practitioners. Treatment with HAART during this early period may not offer definite clinical benefit and is not routinely recommended. Additional clinical studies will be required to determine whether HAART treatment of acute HIV infection is actually beneficial to the patient. However, the period immediately following HIV infection represents an important window of opportunity from a public health perspective characterized by individuals with high infectivity, who are often unaware of their infection status. Thus, identification and counseling of patients with acute HIV infection may be important for preventing the spread of HIV infection to their unaware sexual contacts. This highlights the importance of adequate resources for voluntary counseling and testing programs to help control the spread of the HIV epidemic.



## Summary

Improving the diagnosis of acute HIV-1 infection among healthcare providers remains a priority. It should lead to preventative measures to prevent onward transmission and further research into the mechanisms of HIV-1 transmission. It should also allow to enrol patients into care and decrease the number of late presenters. The impact of very early initiation of ART remains under investigations, and very early cohorts need to be further characterized in term of the potential for maximal immune reconstitution and decrease of viral reservoirs. This should in turn allow to implement new treatment strategies for investigating the potential for virological control post-stopping treatment.

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## Introduction

HIV infection encompasses a spectrum of clinical features ranging from an acute syndrome with primary infection via a prolonged asymptomatic state to advanced disease. The infection relentlessly progresses in untreated patients even during the clinically latent stage. The spectrum of illnesses that one observes changes progressively as the CD4<sup>+</sup> T cell count declines (Fig. 73.1). This correlates with the degree of immunosuppression.

The systemic symptoms in HIV patients can be categorized into the following groups based on the CD4<sup>+</sup> lymphocyte count<sup>1</sup>:

- Greater than 500 cells/ $\mu$ L, causes of systemic symptoms are less likely to be related to HIV infection.
- Between 200 and 500 cells/ $\mu$ L, frequent infections such as bacterial pneumonia and sinusitis occur, however, these are not considered as opportunistic infections (OIs).
- Less than 200 cells/ $\mu$ L, a host of OIs such as cytomegalovirus (CMV), *Strongyloides stercoralis*, *Candida* spp., and *Cryptosporidium parvum* occur.

Common infections can occur with uncommon clinical presentations during this late stage of HIV disease.

## Definition

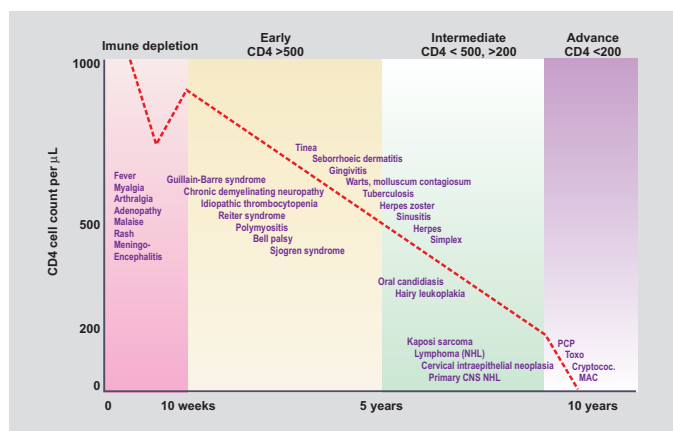
**An OI is an infection caused by pathogens that usually do not cause disease in someone with healthy immune system.** The “opportunity” arises with the compromise of the immune system such as in AIDS. This may also reactivate latent infections which were probably kept in check by the healthy immune system. In this chapter we will deal with OIs in HIV infection/AIDS.

## Pathogenesis

The precipitation of OIs in HIV positive patients is thought to be as a result of severe qualitative and quantitative defects of the CD4<sup>+</sup> T helper lymphocytes.<sup>2,3</sup> The central pathogenic feature of HIV infection is the depletion of CD4<sup>+</sup> T lymphocytes and is largely responsible for the profound immunodeficiency characteristic of the late stages of HIV disease.<sup>4</sup> Multiple mechanisms have been shown to contribute to the HIV-1-associated loss of CD4<sup>+</sup> T cells in HIV-1-infected individuals, among which the HIV-1-induced apoptosis of bystander uninfected cells is considered to be the most important.<sup>5-8</sup> Several virally encoded proteins, including the envelope protein gp120, Tat, and Vpr, have been implicated in this process.<sup>6,9,10</sup> It has recently been seen that CD45, a membrane tyrosine phosphatase, regulates the HIV gp120 mediated apoptosis.<sup>11</sup>

The qualitative defects of the CD4<sup>+</sup> cells weaken the helper role of these cells, both in relation to the monocyte macrophage system and B cell immunoglobulin production.<sup>3</sup> This hampers the chemotaxis and intracellular killing capacity of these cells.<sup>12-14</sup> Thus, HIV-infected individual are predisposed to infections with *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and gram-negative enteric bacteria.

B cell abnormality may present as an increase in the spontaneous secretion of immunoglobulins or as impaired response to a variety of antigens<sup>15</sup> making an individual prone to infection with encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. The lack of antibody response to new infections can be devastating in children with perinatally acquired HIV infection who had no opportunity to develop antibody to infecting pathogen before developing B cell dysfunction.



**Fig. 73.1:** Opportunistic infections in HIV-infected patients in relation to CD4<sup>+</sup> lymphocytes counts.



## Pattern of Infection

OIs were the principal cause of morbidity and mortality before the widespread use of potent combination antiretroviral therapy (ART) in patients infected with HIV. The use of chemoprophylaxis, immunization, and better strategies for managing acute OIs in the early 1990s, contributed to improved quality of life and improved survival.<sup>2</sup> The widespread use of ART starting in the mid-1990s had the most profound influence on reducing OI-related mortality in HIV-infected persons.<sup>16–23</sup> (HOPS & CASCADE study)

OIs, however, continue to cause considerable morbidity and mortality for three primary reasons:

- Many patients seek medical care only when an OI becomes the initial indicator of their disease as they are **unaware** of their HIV infection.
- Certain patients are aware of their HIV infection, but do not take ART because of **psychosocial or economic** factors; and
- Certain patients are prescribed ART, but fail to attain adequate virologic and immunologic response because of factors related to **adherence, pharmacokinetics, or unexplained biologic factors**.<sup>19,24,25</sup>

Recognizing that the relation between OIs and HIV infection is bidirectional is important. HIV leads to immunosuppression that allows opportunistic pathogens to cause disease in HIV-infected persons. OIs and other co-infections that might be common in HIV-infected persons, such as sexually transmitted infections, can also have adverse effects on the natural history of HIV infection. Certain OIs are associated with reversible increases in circulating viral load,<sup>26–29</sup> and these increases could lead to accelerated HIV progression or increased transmission of HIV.<sup>30</sup> Thus, although chemoprophylaxis and vaccination directly prevent pathogen-specific morbidity and mortality, they might also contribute to reduced rate of progression of HIV disease.

In patients infected with HIV, studies have defined the correlation between CD4<sup>+</sup> cell count and occurrence of OIs.<sup>31,32</sup> These were broadly categorized into the following five groups (Table 73.1):

- Asymptomatic infection (CD4<sup>+</sup> cell count > 500/ $\mu$ L)
- Oral candidiasis and tuberculosis (CD4<sup>+</sup> cell count range 250–500/ $\mu$ L)
- Kaposi sarcoma, lymphoma, and *Cryptosporidium* (CD4<sup>+</sup> cell count range 150–200/ $\mu$ L)
- Pneumocystis carinii* (*P. jiroveci*) pneumonia, disseminated *Mycobacterium avium* complex, herpes simplex, toxoplasmosis, cryptococcosis, and esophageal candidiasis (CD4<sup>+</sup> cell count range 75–125/ $\mu$ L)
- CMV retinitis (CD4<sup>+</sup> cell count < 50/ $\mu$ L).

The spectrum of illnesses that one observes changes as the CD4<sup>+</sup> T cell count declines. The more severe and life-threatening complications of HIV infection occur in patients with CD4<sup>+</sup> T cell counts less than 200/ $\mu$ L. Table 73.2 lists some of the infections which are not opportunistic in the true sense but occur in higher frequency than in the general population.

**Table 73.1:** Mean and Median Number of CD4<sup>+</sup> Lymphocytes/ $\mu$ L for Each Category of Opportunistic Infections<sup>31</sup>

Illness	Events No.	CD4 <sup>+</sup> cells Mean	CD4 <sup>+</sup> cells Median
Asymptomatic	20	692.0	575.0
Tuberculosis	7	340.0	159.0
Oral candidiasis	22	275.6	170.0
<i>Cryptosporidium</i>	11	213.0	134.0
Herpes simplex	9	117.6	110.0
Pneumocystosis	70	111.9	70.5
<i>M. avium</i> complex	46	98.4	50.0
Toxoplasmosis	16	93.1	57.5
Cryptococcosis	11	73.2	46.0
Esophageal candidiasis	15	66.5	45.0
CMV retinitis	31	29.0	17.0
Kaposi sarcoma	43	169.5	110.0
Lymphoma	6	166.5	81.5

**Table 73.2:** Infections Occurring in Increased Frequency in HIV Seropositive Individuals

Bacterial
<i>Salmonella</i> spp. <i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Mycobacterium tuberculosis</i> <i>Staphylococcus aureus</i> (most common cutaneous bacterial infection) <i>Pseudomonas aeruginosa</i> (chronic leg ulcers) Sexually transmitted infections such as <i>Treponema pallidum</i> <i>Chlamydia trachomatis</i> <i>Haemophilus ducreyi</i> <i>Calymatobacterium granulomatis</i>
Fungal
<i>Histoplasma</i> spp. <i>Aspergillus fumigatus</i> <i>Nocardia</i> spp. <i>Tinea</i> spp.
Viral
Molluscum contagiosum
Parasitic
<i>Giardia lamblia</i> <i>Sarcoptes scabiei</i>

## True Opportunistic Infections in HIV Patients

### Bacterial and mycobacterial

- *Mycobacterium avium* complex (MAC, MAI)
- Tuberculosis (TB)
- Bacillary angiomatosis (cat scratch disease)

### Fungal infections

- Aspergillosis

- Candidiasis (thrush, yeast infection)
- Coccidioidomycosis
- Cryptococcal meningitis
- Histoplasmosis

### Malignancies

- Kaposi sarcoma
- Lymphoma
  - Systemic non-Hodgkin lymphoma (NHL)
  - Primary central nervous system (CNS) lymphoma
- Progressive multifocal leukoencephalopathy (PML)

### Protozoal infections

- Cryptosporidiosis
- Isosporiasis
- Microsporidiosis
- *Pneumocystis carinii* (*P. jiroveci*) pneumonia (PCP)
- Toxoplasmosis

### Viral infections

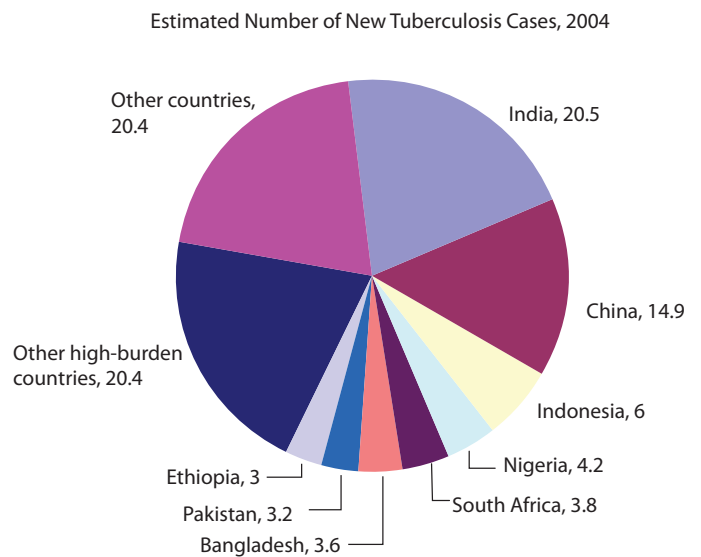
- CMV
- Hepatitis
- Herpes simplex (HSV, genital herpes)
- Herpes zoster (HZV, shingles)
- Human papillomavirus (HPV, genital warts, cervical cancer)
- Molluscum contagiosum
- Oral hairy leukoplakia (OHL)
- PML

The common OIs more relevant to the South Asia are discussed in detail below.

## BACTERIAL

### Mycobacterium Tuberculosis

The World Health Organization (WHO) estimates that TB is the cause of death for 13% of persons with AIDS.<sup>33</sup> Tuberculosis is the most common HIV-related OI in India, and caring for patients with both diseases is a major public health challenge. India has about 1.8 million new cases of TB annually, accounting for a fifth of new cases in the world—a greater number than in any other country (see Fig. 73. 2).<sup>34</sup> Two of every five persons—more than 400 million—have latent TB infection.<sup>35</sup> Tuberculosis can be expected to develop in more than half of those who are also infected with HIV. Between January and September 2006, a total of 15,000 people with suspected TB who were HIV-positive, and 16,420 who were HIV-negative were referred to such facilities by centers in the six Indian states with the highest HIV prevalence (Andhra Pradesh, Karnataka, Maharashtra, Manipur, Nagaland, and Tamil Nadu); TB was diagnosed in 22.3% and 23.9% of patients in these groups, respectively. The estimated incidence of multi-drug resistant TB is 2.4% among patients with new cases and 15% among those who have previously received treatment.<sup>34</sup> High prevalence of HIV infection among individuals with abdominal TB is seen in India.<sup>36</sup>



**Fig. 73.2:** Data are from the World Health Organization. The other high-burden countries, in descending order of number of cases, are the Philippines, Kenya, the Democratic Republic of Congo, Russia, Vietnam, Tanzania, Uganda, Brazil, Afghanistan, Thailand, Mozambique, Zimbabwe, Myanmar, and Cambodia.

The natural history of HIV-1 infection among adults in Mumbai, India, revealed that persons with TB were at 3-fold risk of an early death.<sup>37</sup> The study established the annual incidence of TB at 4.8/100 person-years and a lifetime risk of developing TB as 60% with a consistent correlation between mortality and occurrence of TB.<sup>38</sup>

Data are from the World Health Organization. The other high-burden countries, in descending order of number of cases, are the Philippines, Kenya, the Democratic Republic of Congo, Russia, Vietnam, Tanzania, Uganda, Brazil, Afghanistan, Thailand, Mozambique, Zimbabwe, Myanmar, and Cambodia

Infection with *M. tuberculosis* is almost always acquired by inhalation. A cell mediated immune response normally develops 6–10 weeks after the primary infection and is characterized by the formation of granulomas. Bacilli persist for years, a condition referred to as latent TB infection (LTBI). These people remain well unless there is a breakdown of the immunity.<sup>39</sup> TB disease can develop immediately after exposure (primary disease) or after reactivation of LTBI (reactivation disease). This latent TB is unmasked in HIV-infected people and could explain the higher incidence in the immunocompromised. It is estimated that HIV/TB co-infected individuals have an annual 5–10% chance of reactivation.<sup>40</sup>

Unlike other AIDS-related OIs, CD4+ count is not a reliable predictor of increased risk for TB disease in HIV-infected persons. In patients with relatively high CD4+ T cell counts, the typical pattern of pulmonary reactivation occurs in which patients present with fever, cough, dyspnea on exertion, weight loss, night sweats, and a chest X-ray revealing cavitory apical disease of the upper lobes. In patients

with lower CD4+ T cell counts, disseminated disease is more common. In these patients the chest X-ray may reveal diffuse or lower lobe bilateral reticulonodular infiltrates consistent with miliary spread, pleural effusions, and hilar and/or mediastinal adenopathy. Infection may be present in bone, brain, meninges, gastrointestinal tract, lymph nodes (particularly cervical lymph nodes), and viscera. Extrapulmonary disease is more common in HIV positive patients. Approximately 60–80% of patients have pulmonary disease, and 30–40% have extrapulmonary disease. Respiratory isolation and a negative-pressure room should be used for patients in whom a diagnosis of pulmonary TB is being considered. This approach is critical to limit nosocomial and community spread of infection.<sup>39</sup>

### Management of HIV and Tuberculosis Co-infection

Treatment of TB in HIV-infected patients is similar to those who are seronegative.

The gold standard for diagnosis of TB is microscopy followed by culture and drug sensitivity testing (which is not commonly available). We can use molecular diagnostics to reduce the time required for identifying the organism. It is also useful for infection control.

A high index of suspicion is needed for the diagnosis, and early diagnosis is the key. It is worthwhile to remember that the interpretation of tuberculin skin testing (TST/Mantoux) is not straightforward in patients with HIV infection. The sensitivity of TST is reduced in HIV infection.<sup>39</sup> The diagnostic tools for early diagnosis of TB include regular monitoring with clinical examination of fever, anorexia, weight loss, lymphadenopathy, diarrhea, along with FBC, ESR, Mantoux, radiography of chest, sputum AFB, sputum culture, computerized tomographic scan for CNS or abdominal TB, fine-needle aspiration cytology (FNAC) to rule out other pathogens, and polymerase chain reaction (PCR).

**DOTS (Directly Observed Therapy Short-Course)** It is the preferred form of therapy to prevent relapse and defaulters and thus prevent the occurrence of MDR-TB. The treatment of TB in HIV infected adults is similar to those for HIV uninfected adults. However, there are important exceptions. (BHIVA HIV/TB co-infection guidelines):

- Some intermittent treatment regimens are contra-indicated in HIV-infected patients because of unacceptably high rates of relapse, frequently with organisms that have acquired rifampicin resistance. Consequently, patients with CD4 counts less than 100/ $\mu$ L should receive daily or a minimum of three times weekly anti-TB treatment.
- Adherence strategies including directly observed therapy DOT are especially important for patients with HIV-related TB.
- HIV-infected patients are often taking medication, which might interact with anti-TB medications for example rifampicin, which interacts with antiretroviral agents and other anti-infectives, for example fluconazole.

**Table 73.3:** Suggested Timing of HAART in HIV/TB Co-infection

CD4 count cells/ $\mu$ L	When to treat with HAART
<100	As soon as possible; dependent on physician assessment, (Some physicians delay up to 2 months)
100–200	After 2 months of TB treatment
>200	After completing 6 months TB treatment

(BHIVA TB/HIV Guidelines 2005)

- There are overlapping toxicity profiles and drug–drug interactions with some anti-TB and anti-retroviral drugs that further complicate the concurrent use of HAART and TB treatment.
- There are also concerns about the timing of commencement of HAART in relation to the start of TB treatment in the context of preventing the risk of further HIV progression and the occurrence of paradoxical reactions

The optimal time to start HAART in TB/HIV patients is not known (Table 73. 3). Physicians have to balance the risk of HIV progression if HAART is delayed against the risk of having to discontinue therapies because of toxicities, side effects, paradoxical reactions, or unforeseen drug–drug interactions if HAART is started.

Drug–drug interactions between HIV and TB therapy arise through shared routes of metabolism and are often due to enzyme induction or inhibition.<sup>41,42</sup> One important family of enzymes is the hepatic cytochrome P450 (CYP) system. The non-nucleoside reverse transcriptase inhibitors and protease inhibitors have clinically important drug interactions with the rifamycins, as the latter are potent inducers of CYP3A4.

The inducing effect of rifampicin not only takes at least 2 weeks to become maximal but will also persist for at least 2 weeks after rifampicin has been stopped. If antiretrovirals have been started or changed at the end of TB treatment, this persistent effect on enzyme induction should be taken into consideration. In addition, rifampicin increases the activity of the efflux multi-drug transporter P-glycoprotein (P-gp) that contributes to the elimination of protease inhibitors (PIs).

Until more data are available, low-dose ritonavir/PI combinations should not be given with rifampicin-based regimens. In these cases rifampicin should be substituted for rifabutin, or the protease inhibitor and ritonavir switched to an alternative antiretroviral if alternatives exist.

HIV-seropositive TB group showed an annual mortality of 68% despite adequate TB treatment.<sup>43</sup> Multidrug resistant TB (MDR-TB) and XDR-TB have presented a greater challenge to public health. Resistance to multiple drugs emerges due to (i) inadequate treatment doses, (ii) irregular intake of drugs, (iii) incorrect prescription, and (iv) improper monitoring and supervision. XDR-TB is defined as resistance to at least rifampicin and isoniazid among the first-line anti-TB drugs (which is the definition of MDR-TB) in addition to resistance



**Table 73.4:** Recommended Treatment Regimens for Each Diagnostic Category

TB diagnostic category	TB patients	TB treatment regimens	
		Initial phase (daily or 3 times weekly)	Continuation phase (daily or 3 times weekly)
I	New smear-positive patients New smear-negative pulmonary TB with extensive parenchymal involvement. Severe concomitant HIV disease or severe forms of extrapulmonary TB	2HRZE	4HR or 6HE daily
II	Previously treated sputum smear-positive pulmonary TB: • relapse • treatment after default • treatment failure	2 HRZES/1HRZE	5HRE
III	New smear-negative pulmonary TB (other than in Category I). Less severe forms of extrapulmonary TB.	2HRZE	4HR or 6HE daily
IV	Chronic and MDR-TB (still sputum-positive are suggested for this category after supervised [refer to the current WHO] re-treatment)	Especially designed individualized cases or standardized regimens are suggested for this category	

Note: The numerals in the table represent duration of treatment in months.

Abbreviations: H, INH; R, Rifampicin; E, Ethambutol; Z, Pyrazinamide; S, Streptomycin.

Adapted from World Health Organization. *Treatment of Tuberculosis. Guidelines for National Programmes*. 3rd ed. Geneva, Switzerland, 2003. (WHO/CDS/TB/2003.313)

to any fluoroquinolone, and to at least one of three injectable second-line anti-TB drugs used in TB treatment (capreomycin, kanamycin, and amikacin) (Table 73.4, WHO).

India's national TB control program provides care, diagnosis, and treatment on a huge scale.<sup>44,45</sup> Of course, HIV treatment is often more complex and expensive than TB treatment and must continue indefinitely. When patients with HIV infection are treated at the same facility as those with TB, effective infection-control measures are essential, given the high risk of nosocomial transmission of TB. When caring for co-infected patients, physicians must consider many clinical issues, such as those related to the prevention of disease; the timing of treatment; the choice of medications; drug interactions, side effects, and resistance; and potential re-infection with other mycobacterium strains.

### Mycobacterium Avium-Intracellulare (MAC, MAI)

*Mycobacterium avium* and *Mycobacterium intracellulare* are collectively known as the *Mycobacterium avium* complex (MAC). It is transmitted through inhalation, ingestion, or inoculation via the respiratory or gastrointestinal tract. There is no increased risk of transmission to household or close contacts and person-to-person transmission is unlikely.

In the absence of effective ART or chemoprophylaxis in those with AIDS-associated immunosuppression, the incidence of disseminated MAC disease is 20–40%.<sup>46,47</sup> For persons with a CD4+ count less than 100 cells/ $\mu$ L who are receiving effective prophylaxis or have responded to ART with a sustained increase in CD4+ count to levels greater than 100–200 cells/ $\mu$ L, the overall incidence has been estimated at 2 cases per 100 person-years.

MAC disease typically occurs among persons with CD4+ counts less than 50 cells/ $\mu$ L. Other factors that are associated with increased susceptibility to MAC disease are high plasma HIV RNA levels (>100,000 copies/mL), previous OIs, and previous colonization of the respiratory or gastrointestinal tract with MAC.

MAC disease is typically a disseminated multi-organ infection<sup>48–51</sup> in persons with AIDS not on ART. The early symptoms are minimal and might precede detectable mycobacteremia by several weeks. The symptoms include fever, night sweats, weight loss, fatigue, diarrhea, and abdominal pain.<sup>52</sup>

Localized manifestations of MAC disease have been reported most frequently among persons who are receiving and have responded to ART. They include cervical or mesenteric lymphadenitis, pneumonitis, pericarditis, osteomyelitis, skin or soft tissue abscesses, genital ulcers, or CNS infection.

Laboratory abnormalities particularly associated with disseminated MAC disease include anemia (often out of proportion to that expected for the stage of HIV disease) and elevated liver alkaline phosphatase.<sup>53,55,56</sup> Hepatomegaly, splenomegaly, or lymphadenopathy (paratracheal, retroperitoneal, para-aortic, or less commonly peripheral) might be identified on physical examination or by radiographic or other imaging studies. Other focal physical findings or laboratory abnormalities might occur in the context of localized disease.

Recognition of atypical Mycobacterium is important in the treatment of infections in these patients and in the understanding of epidemiology of atypical mycobacterial infections.

Due to non-availability of diagnostic facilities in developing countries MAC is often under-reported.

HIV-infected adults and adolescents should receive chemoprophylaxis against disseminated MAC disease if they have a CD4+ count of less than 50 cells/ $\mu$ L with azithromycin or clarithromycin which can be discontinued in patients who have responded to ART with an increase in CD4+ counts to greater than 100 cells/ $\mu$ L for more than 3 months. Disseminated MAC can be treated with clarithromycin/azithromycin and ethambutol. Some physicians elect to add a third drug from among rifabutin, ciprofloxacin, or amikacin in patients with extensive disease.<sup>54</sup>

## Bacterial Respiratory Disease

Bacterial pneumonia occurs commonly in HIV-infected patients. Risk factors associated with an increased risk for bacterial pneumonia include low CD4+ count, injection-drug use, and cigarette smoking.<sup>57</sup> *Streptococcus pneumoniae* and *Haemophilus* species are the most frequently identified causes of community-acquired bacterial pneumonia in HIV-infected persons.<sup>58–63</sup> *Pseudomonas aeruginosa* and *Staphylococcus aureus* are also reported as community-acquired pathogens with an increased frequency among persons with HIV infection.<sup>61,64</sup> These persons also have an increased incidence of bacteremia accompanying pneumonia, especially if they are infected with *S. pneumoniae*.<sup>65–67</sup> The clinical and radiographic presentation of bacterial pneumonia in HIV-infected persons is similar to that in persons without HIV infection although they might present with multifocal or multilobar involvement and with parapneumonic effusions more frequently than persons without HIV infection.<sup>68</sup>

No effective means exist to reduce exposure to *Streptococcus pneumoniae* and *Haemophilus influenzae*, which are common in the community. HIV-infected adults and adolescents who have a CD4+ count of greater than 200 cells/ $\mu$ L should be administered a single dose of 23-valent polysaccharide pneumococcal vaccine unless they have received this vaccine during the previous 5 years.

The principles of the treatment of community-acquired bacterial pneumonia are the same for HIV-infected persons as for HIV-uninfected persons.<sup>69</sup>

## Bacterial Enteric Infections

HIV infected people have a 20- to 100-fold higher incidence of gram-negative bacterial enteric infections than the general population.<sup>70–74</sup> *Salmonella* (particularly *Salmonella* serotypes Typhimurium and Enteritidis), *Shigella*, and *Campylobacter* are the most common in adults. The probable source for most HIV-infected associated infections is ingestion of contaminated food or water.<sup>72</sup> *E. coli* seems to be the most common offending organism in developing countries but it does not cause an increased morbidity as compared to *Salmonella*, *Shigella*, and *Campylobacter*.

The three major clinical syndromes of infection with gram-negative enteric bacteria in HIV-infected patients include:

- **Self-limited** gastroenteritis.
- A **more severe and prolonged** diarrheal disease, associated with fever, bloody diarrhea, weight loss, and possible bacter-

emia (bloody diarrhea is more frequent with *Shigella* but also can occur with *Campylobacter* or *Salmonella*).<sup>75,76</sup>

- **Septicemia**, which can exhibit extra-intestinal involvement with or without concurrent or preceding gastrointestinal illness.<sup>77–80</sup>

Recurrent *Salmonella* septicemia constitutes an AIDS-defining illness and might require chronic suppressive therapy.<sup>70</sup>

## Bartonellosis

Three *Bartonella* species (*B. bacilliformis*, *B. quintana*, and *B. henselae*) are currently considered important causes of human disease.

The infections caused by *Bartonella* species include cat scratch disease, trench fever, relapsing bacteremia, endocarditis, bacillary angiomatosis (BA), and bacillary peliosis hepatis.<sup>81</sup> The latter two manifestations occur only in immunocompromised persons. BA is caused by either *B. quintana* or *B. henselae*.<sup>81,82</sup> BA most often occurs late in HIV infection, in patients with a median CD4+ count of less than 50 cells/ $\mu$ L.<sup>82</sup> In HIV-infected patients, bartonellosis is often a chronic illness, lasting for months to years, with BA lesions and intermittent bacteremia.

Development of BA lesions caused by *B. henselae* is statistically linked to cat exposure in patients with HIV infection.<sup>82</sup> In contrast, BA caused by *B. quintana* is associated with body louse infestation and homelessness.<sup>82</sup>

BA lesions are seen in nearly every organ system, but cutaneous lesions are the most readily identified. BA lesions can be clinically indistinguishable from Kaposi sarcoma (KS). BA also can cause subcutaneous nodules. Osteomyelitis is usually caused by *B. quintana*, and only *B. henselae* can cause bacillary peliosis hepatis. Although isolated organs can appear to be the principal focus of disease, BA represents a hematogenously disseminated infection, and systemic symptoms of fever, night sweats, and weight loss often accompany BA. *Bartonella* infection is a major cause of unexplained fever in late-stage AIDS patients and should be considered in the differential diagnosis of patients with fever and a CD4+ count of less than 100 cells/ $\mu$ L.<sup>83</sup>

Diagnosis can be confirmed by histopathologic examination of biopsied tissue.<sup>84</sup> PCR methods have been developed for identification and speciation of *Bartonella*, but are not widely available. This disease, again like MAC infection, is under reported from developing countries owing to lack of diagnostic facilities.

## FUNGAL

### Pneumocystis Pneumonia

*Pneumocystis pneumonia* (PCP) is caused by *Pneumocystis jiroveci*, a ubiquitous organism that is classified as a fungus but that also shares biological characteristics with protozoa. *Pneumocystis carinii* now refers only to the pneumocystis that infects rodents, and *Pneumocystis jiroveci* refers to the distinct species that infects humans. Initial infection with *P. jiroveci* usually occurs in early childhood; two-thirds of healthy children have antibodies to

*P. jiroveci* by age 2–4 years.<sup>85</sup> Approximately 90% of cases occurred among patients with CD4+ counts of less than 200 cells/ $\mu$ L before the use of ART. The other factors associated with a higher risk for PCP included CD4+ cell percentage <14%, previous episodes of PCP, oral thrush, recurrent bacterial pneumonia, unintentional weight loss, and higher plasma HIV RNA.<sup>86,87</sup>

With the widespread use of ART the incidence of PCP has decreased considerably. The majority of cases occur among patients who are unaware of their HIV infection or are not receiving ongoing HIV care<sup>88</sup> or among those with advanced immunosuppression (CD4+ count <100 cells/ $\mu$ L).<sup>89</sup>

Subacute onset of progressive dyspnea, fever, non-productive cough, and chest discomfort that worsens within days to weeks are the most common manifestations of PCP. In mild cases, pulmonary examination is usually normal at rest. With exertion, tachypnea, tachycardia, and diffuse dry ('cellophane') rales might be observed.<sup>90</sup> Oral thrush is a common co-infection. Fever is apparent in the majority of cases and might be the predominant symptom among some patients. Extrapulmonary disease is rare but can occur in any organ and has been associated with use of aerosolized pentamidine prophylaxis.

Hypoxemia is the most characteristic laboratory abnormality. Oxygen desaturation with exercise is indicative of an abnormal alveolar arterial oxygen partial pressure gradient ( $[A-a]O_2$ ) but is non-specific.<sup>91</sup> The chest radiograph typically demonstrates diffuse, bilateral, and symmetrical interstitial infiltrates emanating from the hila in a butterfly pattern; however, patients with early disease might have a normal chest radiograph.<sup>92</sup> Pneumothorax in a patient with HIV infection should raise the suspicion of PCP.<sup>93,94</sup>

High-resolution computerized tomography (CT) demonstrates patchy ground-glass shadows. A definitive diagnosis requires histopathologic demonstration of organisms in tissue, bronchoalveolar lavage fluid, or induced sputum samples,<sup>93,94</sup> as the other common findings are not pathognomonic for PCP. Spontaneously expectorated sputum has low sensitivity and should not be submitted to the laboratory to diagnose PCP.

HIV-infected adults and adolescents, including pregnant women and those on ART, should receive chemoprophylaxis against PCP if they have a CD4+ count of less than 200 cells/ $\mu$ L or a history of oropharyngeal candidiasis.<sup>86,95,96</sup> Persons who have a CD4+ cell percentage of less than 14% or a history of an AIDS-defining illness, but do not otherwise qualify, should be considered for prophylaxis.<sup>86,95,96</sup> When monitoring CD4+ counts frequently (e.g., every 1–3 months) is not possible, initiating chemoprophylaxis at a CD4+ count of greater than 200 cells/ $\mu$ L, but less than 250 cells/ $\mu$ L, should also be considered.<sup>95</sup>

Trimethoprim/sulfamethoxazole (TMP-SMX) is recommended for prophylaxis.<sup>96</sup> One double-strength tablet daily is the preferred regimen. However, one single-strength tablet daily<sup>97</sup> is also effective and might be better tolerated than one double-strength tablet daily. One double-strength tablet three times weekly is also effective.<sup>98</sup> TMP-SMX at a dose of one double-strength tablet daily confers cross-protection against toxoplasmosis and selected common respiratory bacterial infection.

Alternative prophylactic regimens include dapsone, dapsone plus pyrimethamine plus leucovorin, aerosolized pentamidine administered by the Respigard II nebulizer, and atovaquone. Primary pneumocystis prophylaxis should be discontinued for adult and adolescent patients who have responded to ART with an increase in CD4+ counts to greater than 200 cells/ $\mu$ L for more than 3 months. Prophylaxis should be reintroduced if the CD4+ count decreases to less than 200 cells/ $\mu$ L.

TMP-SMX is also the treatment of choice for acute PCP.<sup>99,100</sup> The dose must be adjusted for abnormal renal function. Usual dose is (TMP) 20 mg/kg/day, (SMX) 75–100 mg/kg/day in divided tid/qid. Alternative therapeutic regimens for mild-to-moderate disease include the following:

- (i) Dapsone and TMP
- (ii) Primaquine plus clindamycin
- (iii) Atovaquone suspension. Patients should be tested for **Glucose-6-phosphate dehydrogenase** deficiency whenever possible before administration of primaquine.

Alternative therapeutic regimens for patients with moderate-to-severe disease include clindamycin-primaquine or intravenous (IV) pentamidine<sup>101–103</sup> (usually the drug of second choice for severe disease). Aerosolized pentamidine should not be used for the treatment of PCP because of limited efficacy and more frequent relapse.<sup>102,104,105</sup> The recommended duration of therapy for PCP is 21 days.

## Mucocutaneous Candidiasis

*Candida albicans* causes majority of infections. *C. glabrata* is a cause of refractory mucosal candidiasis in patients with advanced immunosuppression. Extensive, recurrent candidial infection of the gastrointestinal tract, lungs, and skin is observed among severely immunosuppressed individuals.<sup>106–109</sup> A study conducted in Mumbai, India, reported 54% of oral candidiasis among individuals with HIV disease were caused by *Candida tropicalis*.<sup>110</sup>

Patients with CD4+ counts less than 200 cells/ $\mu$ L often present with oropharyngeal or esophageal candidiasis. This is recognized as an indicator of immune suppression.<sup>111</sup> In contrast, vulvovaginal candidiasis is common among healthy, adult women and is unrelated to HIV status.

Oropharyngeal candidiasis is characterized by painless, creamy white, plaque-like lesions of the buccal or oropharyngeal mucosa or tongue surface. Lesions can be easily scraped off with a tongue depressor or other instrument. Less commonly, erythematous patches without white plaques can be seen on the anterior or posterior upper palate or diffusely on the tongue. Angular cheilitis is also noted on occasion and might be caused by *Candida*.

Esophageal candidiasis is occasionally asymptomatic but retrosternal burning pain or discomfort and odynophagia are often present. Endoscopic examination is needed to confirm the diagnosis.

Candida vulvovaginitis is similar to that in normal hosts, and is characterized by a white adherent vaginal discharge associated with mucosal burning and itching. In those with advanced



immunosuppression, episodes might be more severe and more frequently recurrent. Compared with oropharyngeal candidiasis, vaginal candidiasis is less frequent and rarely refractory to azole therapy.

Routine primary prophylaxis is not recommended because mucosal disease is associated with very low attributable mortality, acute therapy is highly effective, prophylaxis can lead to disease caused by drug-resistant species, prophylactic agents can produce drug interactions, and prophylaxis is expensive. ART does reduce the likelihood of mucosal candidiasis.

Oral fluconazole is as effective and may be superior to topical therapy for oropharyngeal candidiasis. Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches and nystatin suspension.<sup>112</sup>

Vulvovaginal candidiasis in HIV-infected women is usually uncomplicated (90%) and responds readily to short-course oral or topical treatment with either of the following:

- Oral fluconazole
- Topical azoles (clotrimazole, miconazole)
- Oral itraconazole

Severe or recurrent episodes of vaginitis require oral fluconazole or topical antifungal therapy for 7 days or more.

## Cryptococcus Neoformans

*Cryptococcus neoformans* is a common OI reported in patients with AIDS in Asia and the Pacific.<sup>106,108,113,114</sup> The majority of HIV-associated cryptococcal infections are caused by *Cryptococcus neoformans* and observed among patients who have CD4+ counts of less than 50 cells/ $\mu$ L.

Cryptococcosis most commonly occurs as a subacute meningitis or meningoencephalitis with fever, malaise, and headache among patients with HIV infection.<sup>115</sup> When cryptococcosis occurs in the HIV-infected patient, disseminated disease is common. Skin lesions mimicking molluscum contagiosum are frequently observed. In addition, isolated pulmonary infection is evident; symptoms and signs include cough and dyspnea in association with an abnormal chest radiograph.

The diagnosis of cryptococcal meningitis is made by identification of organisms in spinal fluid with India ink examination or by the detection of cryptococcal antigen. The serum cryptococcal antigen is also almost always positive in cases of CNS disease and in other instances of disseminated infection. As such, testing for serum cryptococcal antigen is a useful initial screening tool in diagnosing cryptococcosis in HIV-infected patients.<sup>116</sup> Up to 75% of patients with HIV-associated cryptococcal meningitis have routine blood cultures positive for *C. neoformans*.

The recommended initial standard treatment is amphotericin B deoxycholate, at a dose of 0.7 mg/kg daily, combined with flucytosine, at a dose of 100 mg/kg daily in four divided doses, for 2 weeks or more for those with normal renal function. Renal

function should be monitored closely and the flucytosine dose adjusted appropriately for patients with renal impairment.

## Penicillium Marneffeii

Penicilliosis marneffeii (penicilliosis) is caused by the dimorphic fungus *Penicillium marneffeii*, which is endemic in Southeast Asia (especially Northern Thailand) and southern China.<sup>117–119</sup> More recently, 50 indigenous cases of penicilliosis occurred in Manipur, India, identified as a new endemic area of this fungus.<sup>120,121</sup> It is considered an AIDS-defining condition in those parts of the world where it occurs. *P. marneffeii* is the third most common AIDS-defining illness in Thailand, following TB and cryptococcosis. The majority of cases of penicilliosis are observed in patients who have CD4+ counts of less than 100 cells/ $\mu$ L.<sup>122</sup>

Very little was known about the epidemiology and natural reservoir of *P. marneffeii* except that its occurrence increased during the rainy season.<sup>123</sup> Skin lesions, usually papules with central necrotic umbilication, provide the most significant clue to the diagnosis. Cutaneous penicilliosis lesions commonly appear on the face, ears, extremities, and occasionally the genitals.

Disseminated infection presents clinically with generalized lymphadenopathy (90%), hepatomegaly (90%), fever greater than 38.5°C (81%), papular skin lesions with central umbilication (67%), splenomegaly (67%), failure to thrive in children (52%), severe anaemia (43%), and thrombocytopenia (21%).<sup>124</sup> Involvement of other organs such as bone marrow, lymph nodes, lung, liver, and intestine have been reported.

Early diagnosis based on finding *P. marneffeii* in the skin smear or lymph node provides the basis for prompt administration of antifungal therapy.<sup>124</sup> The definitive diagnosis of penicilliosis is based on isolation of organisms from blood culture or other clinical specimens or by histopathologic demonstration of organisms in biopsy material. Many intracellular and extracellular basophilic, spherical, oval, and elliptical yeast-like organisms can be seen, some with clear central septation, which is a characteristic feature of *P. marneffeii*.<sup>125</sup>

*P. marneffeii* is highly susceptible to miconazole, itraconazole, ketoconazole, and 5-flucytosine. Amphotericin B has intermediate antifungal activity, whereas fluconazole is the least active.<sup>126</sup> The recommended treatment is amphotericin B in a dose of 0.6 mg/kg body weight/day administered intravenously for 2 weeks, followed by oral itraconazole in a dose of 400 mg/day for a subsequent duration of 10 weeks. Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for 8 weeks,<sup>127</sup> followed by 200 mg/day for prevention of recurrence. ART should be administered in accordance with standards of care in the community; consideration should be given to simultaneous administration of treatment for penicilliosis and initiation of ART to improve outcome. A study from Chiang Mai University documented that approximately 50% of patients had relapse of

penicilliosis within 6 months after discontinuation of antifungal therapy.<sup>127,128</sup> A double-blind, placebo-controlled study from Chiang Mai, Thailand, demonstrated that oral itraconazole 200 mg daily for secondary prophylaxis in AIDS patients reduced the relapse rate of *Penicilliosis marneffei* from 57% to 0% ( $P < 0.001$ ). All patients who successfully complete treatment for penicilliosis should be administered secondary prophylaxis (chronic maintenance therapy) with oral itraconazole in a dose of 200 mg/day.

Discontinuing secondary prophylaxis for penicilliosis is recommended for AIDS patients who receive combination ART and have CD4+ count greater than 100 cells/ $\mu$ L for 6 months or more. Secondary prophylaxis should be reintroduced if the CD4+ count decreases to less than 100 cells/ $\mu$ L or if penicilliosis recurs at a CD4+ count of greater than 100 cells/ $\mu$ L.

## Aspergillosis

Invasive aspergillosis in the HIV-infected persons is rare. It is most frequently caused by *Aspergillus fumigatus*, although certain cases are caused by *A. flavus*, *A. niger*, and *A. terreus*. Neutropenia, use of corticosteroids, exposure to broad-spectrum antibacterial therapy, and previous pneumonia or other underlying lung disease are specific risk factors. Patients who have had HIV-associated aspergillosis typically have CD4+ count less than 100 cells/ $\mu$ L, a history of other AIDS-defining OIs, and are not receiving ART.

Invasive aspergillosis in the HIV-infected patient is evidenced most commonly as a respiratory illness that can be a necrotizing pneumonia or a tracheobronchitis.<sup>129</sup> Symptoms of invasive pneumonia are fever, cough, dyspnea, chest pain, hemoptysis, and hypoxemia; the chest radiograph might demonstrate a diffuse, focal, or cavitory infiltrate. A “halo” of low attenuation surrounding a pulmonary nodule or an “air-crescent” on CT scan of the lung is suggestive of disease. Extrapulmonary forms of invasive aspergillosis include sinusitis, cutaneous disease, osteomyelitis, and CNS infection.<sup>130</sup>

The diagnosis of pulmonary aspergillosis is usually based on either (i) the repeated isolation of *Aspergillus* spp. from cultures or respiratory secretions or (ii) the finding of dichotomously branching septate hyphae consistent with *Aspergillus* spp. in respiratory or other samples in association with a compatible clinical syndrome. Newer tests based on circulating fungal antigen have been employed to diagnose aspergillosis. A sandwich ELISA test for galactomannan, a major fungal cell wall antigen, can be used on serum and bronchoalveolar lavage fluid.<sup>131</sup>

The recommended treatment for invasive aspergillosis in patients without HIV infection is voriconazole<sup>132</sup> but should be used cautiously with HIV PIs and efavirenz. Amphotericin B deoxycholate at 1 mg/kg daily or lipid-formulation amphotericin B at 5 mg/kg daily are alternatives, as is caspofungin at 50 mg daily and posaconazole. The length of therapy is not established but should continue at least until the peripheral blood CD4+ count is greater than 200 cells/ $\mu$ L and there is evidence of clinical response.

## VIRAL (INCLUDING OPPORTUNISTIC CANCERS)

### Herpes Simplex

Herpes simplex causes primary, secondary, or recurrent genital and extragenital, including oral, lesions. In individuals with severe immunosuppression, recurrent herpes is frequent, likely to be painful, and slow to heal. Orolabial herpes is the most common manifestation of HSV-1 infection. Genital herpes is the most common manifestation of HSV-2 infection. In profoundly immunocompromised patients, extensive, deep, and non-healing genital ulcerations might occur. These lesions have been reported most often in those with CD4+ count of less than 100 cells/ $\mu$ L and also might be more commonly associated with acyclovir-resistant virus.<sup>133</sup> The episodes of genital HSV-1 infection are indistinguishable from genital HSV-2 infection but genital HSV-1 infection recurs less frequently than genital HSV-2 infection.

Non-mucosal HSV infections, such as HSV keratitis, HSV encephalitis, HSV hepatitis, and herpetic whitlow, are similar in presentation to those manifestations observed in HIV-seronegative persons; disseminated HSV infection is rare.

A laboratory diagnosis should be pursued in all cases where possible because mucosal lesions are not diagnosed accurately. PCR is the most sensitive method, but is not widely available. Diagnosis of HSV-2 should be accompanied by counseling that discusses the risk for transmission of infection to sex partners.

Patients with HSV infections can be treated with episodic therapy when lesions occur or with daily therapy to prevent recurrences. Treatment for individual recurrences does not influence the natural history of genital HSV-2 infection and does not reduce the risk for HSV-2 transmission to sex partners, a major concern of persons with genital herpes.

Patients with orolabial lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for 5–10 days. Severe mucocutaneous HSV lesions respond best to initial treatment with IV acyclovir.<sup>133,134</sup> Patients may be switched to oral therapy after the lesions have begun to regress. Therapy should be continued until the lesions have completely healed. Genital HSV infection should be treated with oral valacyclovir, famciclovir, or acyclovir for 5–14 days.

### Varicella Zoster Virus

A person's lifetime risk for herpes zoster is 15–20%, with the highest incidence occurring in the elderly and immunocompromised persons. The incidence of herpes zoster is more than 15-fold higher for HIV-infected adults than for age-matched controls.<sup>135</sup> Herpes zoster can occur in HIV-infected adults at any CD4+ count, but frequency of disease is highest with CD4+ count of less than 200 cells/ $\mu$ L and is not reduced by ART.<sup>136–138</sup>

Herpes zoster manifests as a painful cutaneous eruption in a dermatomal distribution, often preceded by prodromal pain. The most common sites for herpes zoster are the thoracic dermatomes (40–50% of cases), followed by cranial nerve (20–25%), cervical (15–20%), lumbar (15%), and sacral (5%) dermatomes. The

probability of a recurrence of herpes zoster within 1 year of the index episode is approximately 10%.<sup>138,139</sup> Approximately 10–15% of HIV-seropositive patients report post-herpetic neuralgia as a complication following herpes zoster.<sup>140</sup> Most herpes zoster-related complications, including herpes zoster dissemination, occur in patients with CD4+ count of less than 200 cells/ $\mu$ L.<sup>140</sup> The CNS is the primary target organ for herpes zoster dissemination in patients coinfecting with HIV. Various VZV-related neurologic syndromes occur in HIV-infected patients, including CNS vasculitis, multifocal leukoencephalitis, ventriculitis, myelitis and myeloradiculitis, optic neuritis, cranial nerve palsies and focal brain-stem lesions, and aseptic meningitis.

Varicella and herpes zoster are distinctive in appearance and can usually be diagnosed clinically. Varicella can be diagnosed retrospectively by documenting seroconversion. When lesions are atypical or the diagnosis is uncertain, swabs from a fresh lesion or tissue biopsies can be submitted for viral culture, direct fluorescent antigen testing, or PCR, provided facilities are available.

For uncomplicated varicella, recommended treatment options are oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg five times daily), valacyclovir (1 g PO tid), or famciclovir (500 mg PO tid) for 5–7 days. IV acyclovir for 7–10 days (10 mg/kg every 8 hours for 10–14 days) is the recommended initial treatment for HIV-infected patients with severe chickenpox. Prompt antiviral therapy should be instituted in all immunosuppressed herpes zoster patients within 1 week of rash onset or any time before full crusting of lesions. The recommended treatment options for acute localized dermatomal herpes zoster in HIV-infected patients are oral valacyclovir, famciclovir, or acyclovir for 7–10 days.

## Cytomegalovirus Disease

Most clinical disease occurs in previously infected (seropositive) persons and so represent either reactivation of latent infection or reinfection with a novel strain.

End-organ disease caused by CMV occurs among persons with advanced immunosuppression, typically those with CD4+ count less than 50 cells/ $\mu$ L, who are either not receiving or have failed to respond to ART.<sup>141–143</sup> Other risk factors include previous OIs and high plasma HIV RNA levels (>100,000 copies/mL). The incidence of new cases of CMV end-organ disease has declined by 75–80% with the advent of ART.

Retinitis is the most common clinical manifestation of CMV end-organ disease. CMV retinitis occurs as unilateral disease in two-thirds of patients at presentation, but in the absence of therapy or immune recovery, viremic dissemination results in bilateral disease in the majority of patients.<sup>144</sup> For patients with unilateral CMV retinitis and CD4+ count less than 50 cells/ $\mu$ L, rates of contralateral disease approach those of the pre-ART era.<sup>145</sup> CMV retinitis is a full-thickness necrotizing retinitis, and the characteristic ophthalmologic appearance is that of fluffy yellow-white retinal lesions, with or without intraretinal hemorrhage, and with little inflammation of the vitreous unless immune recovery with potent ART intervenes.<sup>141</sup>

Colitis occurs in a small proportion of persons with AIDS and CMV end-organ disease. The most frequent clinical manifestations are fever, weight loss, anorexia, abdominal pain, debilitating diarrhea, and malaise. Extensive mucosal hemorrhage and perforation can be life-threatening complications.

Esophagitis caused by CMV, which occurs in less than 5–10% of persons with AIDS who experience CMV end-organ disease, causes fever, odynophagia, nausea, and occasionally mid-epigastric or retrosternal discomfort. CMV pneumonitis is uncommon. CMV neurologic disease causes dementia, ventriculoencephalitis, or ascending polyradiculomyelopathy.<sup>145</sup> Cerebrospinal fluid (CSF) typically demonstrates lymphocytic pleocytosis (although a mixture of neutrophils and lymphocytes might be evident), low-to-normal glucose levels, and normal-to-elevated protein levels. CMV polyradiculomyelopathy causes a Guillain-Barre-like syndrome characterized by urinary retention and progressive bilateral leg weakness. The clinical symptoms usually progress during several weeks to include loss of bowel and bladder control and to flaccid paraplegia.

CMV viremia can be detected by PCR or antigen assays and is usually observed in end-organ disease, but viremia also might be present in the absence of end-organ disease.<sup>145–150</sup> The presence of serum antibodies to CMV is not diagnostically useful, although a negative IgG antibody level indicates that CMV is unlikely to be the cause of the disease process. The diagnosis of CMV retinitis is usually made based on recognition of characteristic retinal changes observed through a dilated pupil during an ophthalmoscopic examination performed by an experienced ophthalmologist. The diagnosis of CMV esophagitis is established by the presence of extensive large, shallow ulcers of the distal esophagus and biopsy evidence of intranuclear inclusion bodies in the endothelial cells with an inflammatory reaction at the edge of the ulcer.<sup>142</sup>

Oral valganciclovir, IV ganciclovir, IV ganciclovir followed by oral valganciclovir, IV foscarnet, IV cidofovir, and the ganciclovir intraocular implant coupled with valganciclovir are all effective treatments for CMV retinitis. Because ART can control CMV retinitis without anti-CMV therapy in patients who experience immune recovery, some clinicians might consider not treating small peripheral CMV lesions with anti-CMV therapy in ART-naïve patients. IV ganciclovir or foscarnet (or with oral valganciclovir if symptoms are not severe enough to interfere with oral absorption) for 21–28 days form the mainstay of treatment for other CMV infections.

## Oral Hairy Leukoplakia and Epstein–Barr Virus

Oral hairy leukoplakia (OHL) presents as striated white lesions on the lateral margins of the tongue (Table. 73.7), and less frequently on buccal and genital mucosa. It occurs in about 20% of those with asymptomatic HIV infection and becomes more common as the CD4+ count falls.<sup>151</sup>

Diagnosis of OHL is a clinical indicator of rapid disease progression. A study at the University of California showed that 26% of individuals developed oral candidiasis and 42%



developed OHL within 5 years after seroconversion.<sup>152</sup> Another longitudinal study in the US showed that 47% and 67% of individuals developed AIDS within 2 and 4 years of occurrence of OHL, respectively.<sup>153</sup> OHL has been attributed to Epstein-Barr virus (EBV).<sup>154</sup> Several studies in Asia and the Pacific have also reported OHL.<sup>109</sup>

### Non-Hodgkin Lymphoma: Malignancy With Viral Etiology

High-grade B cell non-Hodgkin lymphoma (NHL) is an increasingly important condition in individuals infected with HIV (Table. 73.8).<sup>109,155</sup> It is associated with relatively poor prognosis for survival.<sup>155</sup> CNS NHL occurs more frequently when CD4+ count fall below 50 cells/ $\mu$ L. NHL is possibly due to viral antigenic-mitogenic stimulation leading to cytokine-mediated B cell overproliferation and/or emergence of EBV-infected and immortalized B cells. Fifty percent of these tumors harbour the EBV with a reported equal frequency of EBV A and B subtypes in the tumors.<sup>156</sup>

### Kaposi Sarcoma

Human herpes virus type 8 (HHV-8) is associated with all forms of Kaposi Sarcoma (KS) (i.e., classic, endemic, transplant-related, and AIDS-related) and certain rare neoplastic (e.g., primary effusion lymphoma) and lymphoproliferative disorders (multicentric Castleman disease). The seroprevalence is greater among MSM (20–77%). The precise pathogenesis is unclear even though seroconversion to HHV-8 precedes the development of these tumors.<sup>157</sup>

Malawi, a KS endemic area reports a high titer of HHV-8 in HIV-seropositive men as compared to the HIV-seropositive women.<sup>158</sup> In Asia and the Pacific, where HIV is predominantly transmitted heterosexually, fewer cases of KS have been reported. In decreasing order of frequency, KS is reported in men, women, and children.<sup>155,159–161</sup> Lymph node, oral, gastrointestinal, respiratory, hepatic, and cerebral involvement are reported from the Asia-Pacific region.

Most persons with chronic HHV-8 infection are asymptomatic.<sup>162</sup> Acquisition of HHV-8 has been associated with a primary infection syndrome consisting of fever, rash, lymphadenopathy, bone marrow failure, and occasional rapid progression to KS.<sup>163,164</sup> KS symptoms vary widely, but most persons have non-tender, purplish, indurated skin lesions. Intraoral lesions are common and visceral dissemination can occur, occasionally without the presence of skin lesions.

The introduction of ART since 1995 has reduced the incidence of KS and NHL precipitously.<sup>165</sup> Definitive treatment guidelines do not exist for established KS. Fewer than 10% of AIDS patients with KS die as a consequence of their malignancy, and death from secondary infections is considerably more common. Treatment should be reserved for lesions causing significant discomfort or cosmetic problems. The options are localized

radiation, intralesional vinblastine, or cryotherapy.<sup>166</sup> Systemic therapy with interferon alpha or chemotherapy can be tried for multiple or visceral lesions. Liposomal daunorubicin, liposomal doxorubicin, and paclitaxel are the agents tried.<sup>166–168</sup>

### Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an OI of the CNS, caused by the polyoma virus JC virus (JCV) and characterized by focal demyelination.<sup>169</sup> The virus has worldwide distribution and approximately 85% of adults are seropositive for JCV.<sup>170</sup> Before the advent of potent combination ART, PML eventually occurred in 3–7% of AIDS patients<sup>171,172</sup> but has substantially decreased with the advent of HAART.

PML manifests as focal neurological deficits, usually with insidious onset and steady progression. The MRI almost always confirms distinct white matter lesions in areas of the brain corresponding to the clinical deficits. In contrast to cerebral toxoplasmosis and primary CNS lymphoma, no mass effect or displacement of normal structures is usually evident. JCV DNA by PCR is positive in 70–90% of the cases not taking ART. No established specific therapy exists for JCV infection or PML, and the main approach to treatment involves ART to reverse the immunosuppression that interferes with the normal host response to this virus.

## PROTOZOAL

### Toxoplasmosis

Toxoplasmic encephalitis (TE) is caused by the protozoan *Toxoplasma gondii*. The disease appears to occur almost exclusively because of reactivation of latent tissue cysts.<sup>173–176</sup> Primary infection occasionally is associated with acute cerebral or disseminated disease.

Clinical disease is rare among patients with CD4+ count greater than 200 cells/ $\mu$ L. The greatest risk occurs among patients with a CD4+ count less than 50 cells/ $\mu$ L.<sup>173–175,177</sup> Primary infection occurs after eating undercooked meat containing tissue cysts or ingesting oocysts that have been shed in cat feces and have sporulated in the environment (sporulation requires at least 24 hours). No transmission of the organism occurs by person-to-person contact.

The most common clinical presentation of *T. gondii* infection among patients with AIDS is focal encephalitis with headache, confusion, motor weakness, and fever.<sup>173–175</sup> Physical examination might demonstrate focal neurological abnormalities, and in the absence of treatment, disease progression results in seizures, stupor, and coma. Retinochoroiditis, pneumonia, and evidence of other multifocal organ system involvement can be observed after dissemination of infection but are rare manifestations in this patient population. CT scan or MRI of the brain will typically show multiple contrast-enhancing lesions, often with associated edema.<sup>173,174,178–180</sup> However, toxoplasmosis also can manifest as single lesions in the brain.

HIV-infected patients with TE are almost uniformly seropositive for anti-toxoplasma immunoglobulin G (IgG) antibodies.<sup>173,174</sup> The absence of IgG antibody makes a diagnosis of toxoplasmosis unlikely but not impossible. Anti-toxoplasma immunoglobulin M (IgM) antibodies are usually absent. Quantitative antibody titers are not diagnostically useful. Definitive diagnosis of TE requires a compatible clinical syndrome; identification of one or more mass lesions by CT, MRI, or other radiographic testing; and detection of the organism in a clinical sample. This requires a brain biopsy, which is most commonly performed by a stereotactic CT-guided needle biopsy.

The differential diagnosis of focal neurological disease in patients with AIDS includes CNS lymphoma, mycobacterial infection (especially TB), fungal infection (e.g., cryptococcosis), Chagas disease, bacterial abscess, and rarely PML, which can be distinguished on the basis of imaging studies (PML lesions typically involve white matter rather than gray matter, are non-contrast enhancing, and produce no mass effect).

HIV-infected persons should be tested for IgG antibody to *Toxoplasma* soon after the diagnosis of HIV infection to detect latent infection with *T. gondii*. To minimize risk for acquiring toxoplasmosis, HIV-infected persons should be advised not to eat raw or undercooked meat, including undercooked lamb, beef, and pork. HIV-infected persons should wash their hands after contact with raw meat and after gardening or other contact with soil; in addition, they should wash fruits and vegetables well before eating them raw. If the patient owns a cat, the litter box should be changed daily, preferably by an HIV-negative, non-pregnant person.

*Toxoplasma*-seropositive patients who have a CD4+ count of less than 100 cells/ $\mu$ L should be administered prophylaxis against TE.<sup>181</sup> Prophylaxis against TE should be discontinued among adult and adolescent patients who have responded to ART with an increase in CD4+ count to greater than 200 cells/ $\mu$ L for more than 3 months.

The initial therapy of choice for TE consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin.<sup>182–185</sup> Pyrimethamine penetrates the brain parenchyma efficiently even in the absence of inflammation.<sup>186</sup> Use of leucovorin reduces the likelihood of the hematologic toxicities associated with pyrimethamine therapy.<sup>187,188</sup>

The preferred alternative regimen for patients with TE who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin.

## Cryptosporidiosis

Cryptosporidiosis is caused by various species of the protozoan parasite *Cryptosporidium*, which infect the small bowel mucosa, and in immunosuppressed persons, the large bowel and extra-intestinal sites. Persons at greatest risk for disease have advanced immunosuppression, typically CD4+ count of less than 100 cells/ $\mu$ L.<sup>189</sup> The three most common species infecting humans are *C. hominis*, *C. parvum*, and *C. meleagridis*. Infection occurs through ingestion of *Cryptosporidium* oocysts. Chronic diarrhea

due to *C. parvum* is reported in 20 to 25% of patients with AIDS in India.<sup>190–192</sup>

Patients with cryptosporidiosis most commonly have acute or subacute onset of profuse, non-bloody, watery diarrhea, accompanied often by nausea, vomiting, and lower abdominal cramping.<sup>193</sup> Fever is present in approximately one-third of patients and malabsorption is common. The epithelium of the biliary tract and the pancreatic duct can be infected with *Cryptosporidium*, leading to sclerosing cholangitis and to pancreatitis secondary to papillary stenosis, particularly among patients with prolonged disease and low CD4+ counts.<sup>194–197</sup>

Diagnosis of cryptosporidiosis can be made by microscopic identification of the oocysts in stool or tissue. *Cryptosporidium* oocysts also can be detected by direct immunofluorescence, which offers the greatest sensitivity and specificity, or by enzyme-linked immunosorbent assay (ELISA).<sup>198</sup>

Scrupulous handwashing can reduce the risk for diarrhea in HIV-infected persons, including diarrhea caused by *Cryptosporidium*.<sup>199</sup> Water should be boiled before drinking as the most simple measure.

In the setting of severe immunosuppression, ART with immune restoration to a CD4+ count greater than 100 cells/ $\mu$ L leads to resolution of clinical cryptosporidiosis.<sup>200</sup> and is the mainstay of treatment. Therefore, patients with cryptosporidiosis should be offered ART as part of the initial management of their infection. Multiple agents have been investigated in small, randomized controlled clinical trials on HIV-infected adults, including nitazoxanide, paromomycin, spiramycin, bovine hyperimmune colostrum, and bovine dialyzable leukocyte extract.

## Microsporidium

Microsporidia are related to fungi, defined by the presence of a unique invasive organelle consisting of a single polar tube that coils around the interior of the spore.<sup>201,202</sup> In the immunosuppressed host, clinical signs related to microsporidiosis are most commonly observed when the CD4+ count is less than 100 cells/ $\mu$ L.<sup>201–203</sup> The most common manifestation of microsporidiosis is gastrointestinal tract infection with diarrhea; however, encephalitis, ocular infection, sinusitis, myositis, and disseminated infection also are described.<sup>201,203</sup> Effective morphologic demonstration of microsporidia by light microscopy can be accomplished by staining methods that produce differential contrast between the spores of the microsporidia and the cells and debris in clinical samples (e.g., stool). In biopsy specimens, microsporidia can be visualized with Giemsa, tissue Gram stains (Brown–Hopps Gram stain), calcofluor white or Uvitex 2B (fluorescent brighteners) staining, Warthin–Starry silver staining, hematoxylin and eosin, or Chromotrope 2A.<sup>204</sup>

Patients with AIDS (e.g., CD4+ count less than 200 cells/ $\mu$ L) should avoid untreated water sources. Otherwise, other than general attention to handwashing and other personal hygiene measures, no precautions to reduce exposure to microsporidia are recommended.

ART with immune restoration (an increase of CD4<sup>+</sup> count to > 100 cells/ $\mu$ L) is associated with resolution of symptoms of enteric microsporidiosis, including that caused by *E. bieneusi*.<sup>200,205–207</sup>

## Leishmaniasis

Leishmaniasis is caused by obligate intracellular protozoa that survive and replicate in intracellular vacuoles within macrophages. The *Leishmania* genus has traditionally been differentiated into multiple species that cause cutaneous, mucosal, or visceral disease.<sup>208,209</sup> Leishmaniasis among persons with HIV/AIDS has been reported primarily from Spain, Italy, France, Brazil, and Ethiopia, but most coinfections in the developing world are never reported.<sup>210</sup> The incidence has decreased substantially in developed countries with the introduction of ART<sup>211,212</sup>; however, HIV-leishmaniasis coinfection poses a growing problem in Asia and Africa.<sup>213,214</sup>

After primary infection, *Leishmania* remain viable in healthy persons for long periods, leading to a susceptible population if immunosuppression occurs. In HIV-infected persons without severe immunosuppression, disease manifestations are similar to those in immunocompetent persons. Among those with advanced immunosuppression and low CD4<sup>+</sup> counts (<200 cells/ $\mu$ L), manifestations of leishmaniasis might be both atypical and more severe, and relapse after treatment is common.<sup>215</sup>

The most common clinical presentation of leishmaniasis in persons with AIDS is a disseminated visceral disease syndrome, but the distribution varies geographically, reflecting differences in the predominant parasite species. Among persons with visceral disease, the most common clinical and laboratory findings are fever (65–100%), systemic malaise (70–90%), splenomegaly (usually moderate, 60–90%), hepatomegaly without splenomegaly (34–85%), hepatosplenomegaly (68–73%), lymphadenopathy (12–57%), and pancytopenia (50–80%). Anemia is usually marked with less than 10 g hemoglobin/dL (49–100%), leukopenia moderate with less than 2400 leukocytes/ $\mu$ L (56–95%), and thrombocytopenia is usually present (52–93%). Splenomegaly is somewhat less common in HIV-coinfected patients than in immunocompetent patients with visceral leishmaniasis.<sup>216</sup>

Demonstration of characteristic amastigote forms of *Leishmania* by histopathology, cultures, and smears in tissue specimens (e.g., scrapings, aspirates, and biopsies) is the standard for diagnosis of cutaneous leishmaniasis among HIV-coinfected patients.<sup>217</sup> The diagnosis of visceral leishmaniasis can also be made by the demonstration of amastigote forms in cultures from the peripheral blood, and smears or cultures from bone marrow or splenic aspirates. Other methods useful for demonstrating *Leishmania* in the blood or tissue of coinfecting patients include detection of *Leishmania* nucleic acid by PCR amplification (>95% sensitivity).<sup>218</sup>

Antibodies against *Leishmania* antigens are of high sensitivity for the diagnostic value among immunocompetent patients with visceral disease.<sup>219</sup> However, the sensitivity of serologic tests is substantially lower in HIV-coinfected patients.<sup>220</sup> The use of

recombinant antigen (e.g., rK39) in ELISA assays might increase sensitivity, but a proportion of coinfecting patients will remain seronegative.<sup>221</sup>

For HIV-visceral leishmaniasis-coinfecting patients, the efficacy of conventional and lipid-associated formulations of amphotericin B appears to be similar to that of pentavalent antimony. However, liposomal and lipid complex preparations are substantially better tolerated than conventional amphotericin B or pentavalent antimony.<sup>222–224</sup>

## Management Of Opportunistic Infections: General Principles to Consider

Clinicians treating HIV-infected patients often have to consider two questions related to OIs and ART:

- (i) When to initiate ART in ART-naïve persons who experience an acute OI.
- (ii) How ART should be managed for persons who are on ART but who experience an acute OI.

Initiation of ART has been documented to be effective for OIs for which effective therapy does not exist for example, cryptosporidiosis, microsporidiosis, and PML.<sup>225–227</sup> For KS, initiation of ART has been documented to lead to resolution of lesions in the absence of specific therapy for the sarcoma.<sup>228</sup> It also has preventive benefit—a second OI is less likely to occur if ART is started promptly rather than delaying the initiation of ART.

The disadvantages of starting ART in a setting of OI are many. There may be failure to absorb the ART drugs leading to subtherapeutic serum levels and development of antiretroviral drug resistance. ART toxicities might be confused with disease manifestations or toxicities associated with drugs used for treating patients with an OI. Drug–drug interactions among ART and anti-OI drugs might be difficult to manage. Renal or hepatic dysfunction during acute OIs might make dosing of ART drugs difficult to estimate. Finally, IRIS (see below) events can occur and cause manifestations that are difficult to distinguish from other clinical conditions.

For these reasons, no consensus has been reached concerning the optimal time to start ART in the setting of a recently diagnosed OI. However, one recently completed randomized clinical trial has demonstrated a clinical and survival benefit of starting ART early, within the first 2 weeks, of initiation of treatment for an acute OI, excluding TB.<sup>229</sup>

OIs that occur after patients have been started on ART can be categorized into three groups. The first group includes OIs that occur shortly after initiating ART (within 12 weeks). These cases might be subclinical infections that have been unmasked by early immune reconstitution or simply OIs that occurred because of advanced immunosuppression and are not considered to represent early failure of ART. Many of these cases represent IRIS.<sup>230–235</sup>

The second group includes OIs that occur more than 12 weeks after initiation of ART among patients with suppressed



**Table 73.5:** Recommendations for Minimizing Exposure to Selected Pathogens among Patients with HIV Infection

Pathogen	Potentially effective intervention
<i>Pneumocystis jiroveci</i>	Avoid close contact with patients who have active <i>P. carinii</i> pneumonia (e.g., avoid sharing hospital room)
<i>Toxoplasma gondii</i>	Avoid eating undercooked red meat and exposure to cats that scavenge for food outdoors
<i>Cryptosporidium</i>	Avoid drinking unprocessed ground water (e.g., from lakes or streams); use properly boiled, bottled, or filtered water; avoid household pets less than 6 months of age, especially those that were obtained from commercial breeders or pet shelters, that were previously strays, or that have diarrhea; emphasize good hygiene in child care
<i>Mycobacterium tuberculosis</i>	Avoid high-risk occupational settings, such as correctional facilities, homeless shelters, and certain healthcare situations
CMV	If patient is seronegative for CMV, avoid transfusion with CMV-seropositive or unfiltered blood products; avoid unprotected sexual exposure. Emphasize good hygiene in child care
Human papillomavirus, herpes simplex virus, and Hepatitis B	Avoid unprotected sexual exposure Immunisation

HIV RNA levels and sustained CD4+ count greater than 200 cells/ $\mu$ L.<sup>236,237</sup> Determining whether these represent a form of IRIS rather than incomplete immunity with the occurrence of a new OI is difficult. The third group includes OIs that occur among patients who are experiencing virologic and immunologic failure while on ART. These represent clinical failure of ART.

When an OI occurs within 12 weeks of starting ART, treatment for the OI should be started and ART should be continued. When an OI occurs despite complete virologic suppression (i.e., late OI),

therapy for the OI should be initiated and ART should be continued. If the CD4+ response to ART has been suboptimal, modification of the ART regimen may be considered, although no evidence exists to indicate that changing the ART regimen in this setting will improve the CD4+ response. When an OI occurs in the setting of virologic failure, OI therapy should be started, antiretroviral resistance testing should be performed, and the ART regimen should be modified, if possible, to achieve better virologic control.

Tables 73.5, 73.6, 73.7, and 73.8 summarize the management of OIs in HIV patients (Adapted from Kovacs JA, Masur H. Prophylaxis against opportunistic infections in patients with human immunodeficiency virus infection. *NEJM* 2000;342:1416–29).

### Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS consists of several distinct disorders that appear to result from dysfunction of those aspects of immune reconstitution that affect restoration of pathogen-specific immune responses and/or immune regulation.<sup>238</sup>

It is the paradoxical deterioration in clinical status after ART initiation despite improved immune function. It typically occurs in patients with low initial CD4 (usually <50) and a rapid decline in viral load. The usual onset is within 6 weeks of ART initiation, but sometimes several months later.<sup>239–241</sup>

Immune reconstitution is usually seen with infections with *M. avium* complex, *M. tuberculosis* (30% of cases), and other mycobacteria, CMV, *Cryptococcus*, PCP, Leishmania, HSV, VZV, Hepatitis B & C, JC virus, HHV 8, and others.

It can present with fever, localized lymphadenopathy/lymphadenitis, abscesses, pneumonia, vitritis, CNS disease, hepatitis, and dermatologic manifestations. Presentations of OIs may be atypical.

MAC: Granulomatous lymphadenopathy without mycobacteremia.

CMV: Vitritis.

PML: enhancing CNS lesions.

*Cryptococcosis*: marked CSF leukocytosis.

**Table 73.6:** Drug Regimens for Primary Prophylaxis against OIs in Patients with HIV Infection

Pathogen	First choice	Alternatives
<i>Pneumocystis jiroveci</i>	Trimethoprim–sulfamethoxazole, 1 double strength tablet orally per day or 1 single strength tablet orally per day	Trimethoprim–sulfamethoxazole, 1 double-strength tablet orally 3 times a week; Dapsone, 50 mg orally twice a day or 100 mg orally per day; Dapsone, 50 mg orally per day, plus pyrimethamine, 50 mg orally once a week, plus leucovorin, 25 mg orally once a week; Dapsone, 200 mg orally once a week, plus pyrimethamine, 75 mg orally once a week, plus leucovorin, 25 mg orally once a week; Atovaquone, 1500 mg orally per day; Aerosolized pentamidine, 300 mg monthly by Respigard II nebulizer
<i>Toxoplasma gondii</i>	Trimethoprim–sulfamethoxazole, 1 double-strength tablet orally per day	Trimethoprim–sulfamethoxazole, 1 single-strength tablet orally per day; Dapsone, 50 mg orally per day, plus pyrimethamine, 50 mg orally once a week, plus leucovorin, 25 mg orally once a week; Atovaquone, 1500 mg orally per day
<i>M. avium</i> complex	Azithromycin, 1200 mg orally once a week; or Clarithromycin, 500 mg orally twice a day	Rifabutin, 300 mg orally per day; Azithromycin, 1200 mg orally once a week, plus rifabutin, 300 mg orally per day

**Table 73.7:** Drug Regimens for Secondary Prophylaxis against OIs after Chemotherapy for Acute Infection in Patients with HIV Infection

Pathogen	First choice	Alternatives
<i>Pneumocystis jiroveci</i>	Trimethoprim–sulfamethoxazole -1 double strength tablet orally per day or 1 single strength tablet orally per day	Same as primary
<i>Toxoplasma gondii</i>	Sulfadiazine, 500–1000 mg orally 4 times a day, plus pyrimethamine, 25–75 mg orally per day, plus leucovorin, 10 mg orally per day	Clindamycin, 300 mg orally 4 times a day or 450 mg orally 3 times a day, plus pyrimethamine, 25–75 mg orally per day, plus leucovorin, 10–25 mg orally per day
<i>Mycobacterium avium</i> complex	Clarithromycin, 500 mg orally twice a day, plus ethambutol, 15 mg/kg of body weight orally per day, with or without rifabutin, 300 mg orally per day	Azithromycin, 500 mg orally per day, plus ethambutol, 15 mg/kg orally per day, with or without rifabutin, 300 mg orally per day
CMV	Ganciclovir, 5–6 mg/kg intravenously 5–7 days a week or 1000 mg orally 3 times a day; Valganciclovir 900 mg bid PO Foscarnet, 90–120 mg/kg intravenously per day; (for retinitis) ganciclovir sustained-release implant, every 6–9 mo, plus ganciclovir, 1000 to 1500 mg orally 3 times a day	Cidofovir 5 mg/kg every other week IV + Probenecid Fomivirsen 330 mg intravitreal q2–4 wk Valganciclovir 900 mg PO daily
<i>Cryptococcus neoformans</i>	Fluconazole, 200 mg orally per day	Itraconazole 200 mg/d PO
Salmonella species (not <i>S. typhi</i> ) bacteremia	Ciprofloxacin, 500 mg orally twice a day for 6–8 months	None
Herpes simplex virus	None; if recurrences are severe or frequent, consider acyclovir, 200 mg orally 3 times a day or 400 mg orally twice a day	Famciclovir, 500 mg orally twice a day; Valacyclovir, 500 mg orally twice a day
Candida oropharyngeal, oesophageal, or vaginal)	None; if recurrences are severe or frequent, consider fluconazole, 100–200 mg orally per day	Itraconazole, 200 mg orally per day
<i>Penicillium marneffei</i>	Itraconazole 200 mg/d PO	-

**Table 73.8:** Recommendation for Initiating and Discontinuing Primary and Secondary Prophylaxis for Adults and Adolescents with HIV Infection

Pathogen	Primary prophylaxis			Secondary prophylaxis		
	Start	Stop	Restart	Start	Stop	Restart
<i>Pneumocystis jiroveci</i>	CD4 cell count <200/ $\mu\text{m}^3$ or oropharyngeal candidiasis	CD4 cell count >200/ $\mu\text{m}^3$ for 3–6 mo	Same as to start	Prior <i>P. jiroveci</i> pneumonia	CD4 cell count >200/ $\mu\text{m}^3$ for 3–6 mo	Same as for primary prophylaxis
<i>Toxoplasma gondii</i>	CD4 cell count <100/ $\mu\text{m}^3$ and IgG antibodies to toxoplasma	Follow <i>P. jiroveci</i> pneumonia guidelines, since all agents other than aerosol pentamidine will have some activity	Follow <i>P. jiroveci</i> pneumonia guidelines	Prior toxoplasmosis	Lifelong*	NA
<i>M. avium</i> complex	CD4 cell count <50/ $\mu\text{m}^3$	CD4 cell count >100/ $\mu\text{m}^3$ for 3–6 mo	Same as to start	Prior <i>M. avium</i> complex disease	Lifelong*	NA
CMV	Not recommended	NA	NA	Prior CMV disease	CD4 cell count >100–150/ $\mu\text{m}^3$ for 3–6 mo; non-sight-threatening lesion, adequate vision in other eye, and regular eye examination	CD4 cell count <50/ $\mu\text{m}^3$
Herpes simplex virus, varicella–zoster virus, candida species, <i>Cryptococcus neoformans</i> , <i>Histoplasma capsulatum</i> , <i>Coccidioides immitis</i>	Not recommended	NA	NA	Recommended only for prior cryptococcal, histoplasma, or coccidioides disease	Lifelong for cryptococcal, histoplasma, or coccidioides disease*	NA

\*The data available are not sufficient to stop secondary prophylaxis.

Autoimmune diseases may be exacerbated. In active TB although there is a high risk of paradoxical worsening after initiation of ART, the overall mortality is improved in coinfecting patients with CD4 greater than or equal to 100/ $\mu$ L treated with ART.<sup>242,243</sup>

Diagnosis of IRIS is clinically challenging and involves differentiation from progression of the initial OI (including the possibility of antimicrobial resistance and treatment failure), development of a new OI, unrelated organ dysfunction, or drug toxicity.

Therapy for IRIS has been empiric. No well-controlled trials exist to help decide when non-steroidal drugs or corticosteroids are needed or when ART should be suspended. The inflammation might take weeks or months to subside. IRIS does not appear to have favorable or unfavorable implications about patient survival, with the possible exception of IRIS associated with cryptococcal meningitis.<sup>240,244</sup>

The general principles include the following:

- Treating the underlying active infection
- Continue ART, unless inflammatory response is life threatening
- Anti-inflammatory therapy (NSAIDs and/or corticosteroids)
- Response to corticosteroids typically rapid. Slow taper may be required
- Initiation of ART during the treatment of active OIs is controversial. Timing of ART depends on severity of OI and degree of immunosuppression.

## SPECIFIC MEASURES

**MAC (Lymphadenitis):** NSAIDs initially; if symptoms persist steroids may be indicated. Surgical drainage may be needed for abscesses.

**M. tuberculosis:** Steroids for 2 weeks with slow taper. TB should be treated for more than 2 months before HAART unless CD4 less than 100.

**CMV vitritis:** Systemic or periocular steroids.

**Hepatitis:** HBV co-infection consider using Tenofovir with Lamivudine or Emtricitabine.

**Cryptococcal meningitis:** Steroids and serial LPs to manage elevated CSF pressure.

## Conclusion

In Asia and the Pacific region, fewer clinicians are willing to provide care and support to persons living with HIV/AIDS. The laboratory infrastructure required for identification of OIs is grossly inadequate. Hence, most published reports present frequency of syndromes such as chronic diarrhoea, weight loss greater than 10% of body weight, recurrent fever, chronic cough, persistent headache, and cutaneous manifestations caused by a host of OIs. It is up to the clinicians to reach a

diagnosis with the available limited resources, unlike in the developed countries and this is what makes it more challenging as well as interesting.

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## Mucocutaneous Manifestations of HIV

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### Introduction

The skin, being the most visible and largest organ, often shows early manifestations of internal disease; same holds true for human immunodeficiency virus (HIV) disease. Skin is the most commonly affected organ in patients with HIV/AIDS with more than 90% of HIV-infected patients developing cutaneous signs and symptoms. Cutaneous manifestations can occur through all stages of HIV infection. Dermatological diseases in HIV are a spectrum of inflammatory, infectious, and oncogenic disorders. They are in most of the situations diagnostic markers of HIV infection and opportunistic infections. Severe opportunistic infections may present for the first time in the skin.<sup>1</sup> They have specific prognostic significance independent of other markers, and are more helpful in situations where facilities for CD4 count and viral load are not easily available to monitor the progression of the disease.

Dermatological manifestations may also be cosmetically disfiguring and source of severe morbidity, both physical and psychological. The skin lesions in seropositive patients may be atypical and response to treatment may be poor. In addition, the HIV epidemic has brought to attention previously rare and poorly understood skin diseases, such as bacillary angiomatosis, Kaposi sarcoma, and eosinophilic folliculitis.

Mucocutaneous disorders of HIV should thus be considered among key clinical indicators for prediction of underlying immune status as well as immune reconstitution inflammatory syndrome (IRIS).

There is a tremendous change observed in the mucocutaneous manifestations in pre-ART and post-ART era. In the pre-ART era, numerous and varied opportunistic infections, malignancies and DNA viral infections were common. Most cutaneous manifestations of HIV infection clear spontaneously with ART. In the ART era, mucocutaneous manifestations have been replaced by antiretroviral therapy (ART)-related adverse drug reactions (ADR) and endocrinal and metabolic changes. Dermatologists should be well-grounded in the diagnosis and treatment of these conditions.<sup>2</sup>

### Skin and HIV Interaction

The skin-specific immune surveillance system includes antigen-presenting Langerhans cells, dermal and epidermal T lymphocytes, cytokine-producing keratinocytes, and draining peripheral lymph nodes. In the HIV-1 infected, this surveillance system appears to be compromised, as evidenced by a reduction in the epidermal Langerhans cell population. Because human epidermal Langerhans cell expresses surface-bound CD4 antigens, HLA-DR antigens, and Fc-IgG receptors, all of which are involved in HIV-1 binding to, or entry into, the target cell; the reduction in Langerhans cells in patients with acquired immunodeficiency syndrome (AIDS) may be a direct consequence of HIV-1 infection and consequent injury to Langerhans cells leading to decreased Langerhans cell function.<sup>3</sup>

Preputial skin contains lot of Langerhans cells. These cells are the prime targets for HIV. Impairment of skin immune system is responsible for mucocutaneous manifestations even before the development of complete immunodeficiency.

### Classification

As stated previously, mucocutaneous manifestations occur during all stages of HIV infection and they can be inflammatory, infectious, oncogenic or non-specific in nature. A brief classification of the various mucocutaneous manifestations is given; there can be a combination of any of the inflammatory or infectious disorders and in a given patient, more than one infectious agent may be responsible for the final clinical picture.

#### A. Infectious manifestations

1. Viral infections
  - (a) Acute exanthema of HIV
  - (b) Herpes simplex virus (HSV)/varicella zoster virus (VZV)
  - (c) Epstein-Barr virus (EBV)/cytomegalovirus (CMV)
  - (d) Human papillomavirus (HPV)
  - (e) Molluscum contagiosum

- (f) Others: Hepatitis B/C, human T-cell lymphotropic virus (HTLV)
- 2. Bacterial infections
  - (a) *Staphylococcus aureus*
  - (b) Mycobacterial infection
  - (c) Bacillary angiomatosis
- 3. Fungal infections
  - (a) Dermatophytosis
  - (b) Candidiasis
  - (c) Other superficial mycoses—*Malassezia furfur*, Trichosporosis
  - (d) Deep and systemic mycoses—Cryptococcosis, histoplasmosis, penicilliosis
- 4. Parasitic infections
  - (a) Arthropod infections—Scabies and demodicidosis
  - (b) Protozoal infections—Pneumocystosis, toxoplasmosis, leishmaniasis

## B. Non-infectious dermatoses

- 1. Papulosquamous disorders
  - (a) Ichthyosiform dermatitis—dryness, eczema
  - (b) Seborrheic dermatitis
  - (c) Psoriasis
  - (d) Reiter disease
- 2. Pruritic eruptions of HIV
  - (a) Follicular
    - (i) Eosinophilic folliculitis
    - (ii) Demodex folliculitis
    - (iii) Pityrosporum folliculitis
  - (b) Non-follicular
    - (i) Papular
    - (ii) Eczematous
  - (c) Papular pruritic eruptions (PPE)
  - (d) Others—Pruritus in HIV
- 3. Pigmentary disorders
- 4. Cutaneous adverse drug reactions (ADR)
- 5. Neoplasms—Kaposi sarcoma, lymphoma
- 6. Miscellaneous—Pityriasis rubra pilaris (PRP), immune thrombocytopenic purpura (ITP), pityriasis rosea (PR), photosensitivity

## C. Cutaneous adverse drug reactions (ADR) of ART

### D. Specific mucosal manifestations

- 1. Gingivitis/periodontitis
  - (a) Linear gingival erythema
  - (b) Necrotizing ulcerative periodontitis
- 2. Angular cheilitis
- 3. Necrotizing stomatitis
- 4. Autoimmune/idiopathic
  - (a) Recurrent aphthae
  - (b) Immune thrombocytopenic purpura (ITP)
  - (c) Salivary gland disease

- (d) Abnormal pigmentation
- 5. Tuberculosis
- 6. Viral
  - (a) Oral hairy leukoplakia (OHL)
  - (b) Herpes simplex virus (HSV)
  - (c) Herpes zoster virus (HZV)
  - (d) Human papillomavirus (HPV)
- 7. Fungal
  - Oral candidiasis
- 8. Malignancy
  - (a) Kaposi sarcoma (KS)
  - (b) Non-Hodgkin lymphoma (NHL)

### E. Hair manifestations

- 1. Premature graying of hair
- 2. Diffuse hair loss
- 3. Male pattern alopecia
- 4. Alopecia areata
- 5. Long eyelashes

### F. Nail manifestations

- 1. Onychomycosis
- 2. Yellowish discoloration
- 3. Melanotic bands
- 4. Black pigmentation—due to zidovudine (AZT)

## VIRAL INFECTIONS

### Acute Exanthem of HIV Seroconversion Illness

Acute exanthem accompanied by HIV seroconversion refers to an acute viral prodrome with cutaneous eruptions. Acute primary HIV infection/seroconversion may go unnoticed, unreported or undiagnosed. It usually lasts for a few days. There is a symmetrical maculopapular erythematous exanthem of face, palms, and soles found in 75% of the persons with symptomatic seroconversion.<sup>4</sup> It may occasionally manifest as exanthem, urticaria, toxic erythema, erythema multiforme (EM), oropharyngeal candidiasis, acute genitocrural intertrigo, and oral or genital ulcerations. More severe and numerous the manifestations, and more prolonged the duration; more likely is the rapid progression of HIV disease.

### Herpes Simplex Virus

Herpes simplex viral infection is one of the most common opportunistic infections in the HIV-infected patients. It can be symptomatic or an asymptomatic carrier state. HIV type 1 (HIV-1)-infected persons have high rates of HSV type 2 (HSV-2) infection, ranging from 50% to 90% in studies of HIV-infected populations from different parts of the world.<sup>5</sup> HIV and HSV are co-transmitters of each other. There is 3–4 fold rise in plasma HIV load during acute outbreaks of HSV infection and there is two-fold increased risk of HIV acquisition in patients having genital herpes due to mucosal barrier disruption and presence of activated T lymphocytes



**Fig. 74.1:** Giant genital herpes.

in the ulcer base.<sup>6</sup> HIV-positive patients with HSV infection shed more herpes simplex virus from genital mucosal tract even in the absence of clinical herpes.

Presence of chronic herpetic ulcers of longer than 1 month duration is an AIDS defining condition. Tender, often painful ulcerative lesions of genital region, perianal area and lip are the hallmark of HSV in HIV-infected patients (Fig. 74.1). Anogenital erosions may progress to chronic, crusted, vegetative or ulcerative lesions. HSV reactivation occurs significantly more often and most of these reactivations are perirectal and subclinical. As the immunodeficiency progresses, HSV infection becomes chronic, persistent, progressive and recurrent, responding less promptly to oral antiviral therapy.

Loss of nail due to herpetic infection may occur. HSV can cause persistent necrotic digits—"herpetic whitlow" (Fig. 74.2 a&b) and perioral ulceration, which may spread to oropharynx, oesophagus, and cause odynophagia. Follicular facial lesions have also been reported. In a study of 200 HIV-positive cases Marfatia et al.<sup>6</sup> reported cryptic herpes presenting as herpetic esophagitis in 0.5% and herpetic cervicitis in 1% cases. Secondary bacterial infection is almost always seen. Concomitant infection with CMV in the form of hyperkeratotic verrucous lesions has been observed. Serious clinical complications of HSV in the presence of HIV are dissemination, encephalitis, and development of acyclovir resistance.

Diagnosis of herpes requires high index of suspicion, particularly in atypical presentation and subclinical reactivation. Tzanck smear and biopsy for acantholytic cells and multinucleate giant cells are performed to confirm the diagnosis. Viral culture or polymerase chain reaction (PCR) needs to be performed for a definitive diagnosis. Electron microscopy of fresh lesional fluid, DNA hybridization, immunofluorescence, and sera for HSV antibodies can be examined to support the diagnosis.<sup>4</sup>

HSV and HIV co-infection is often referred to as double trouble. Thereby, aggressive treatment of herpetic ulcers is of vital importance in HIV management. Early administration of 200 mg acyclovir five times a day is known to suppress HSV2 reactivation (Fig. 74.3



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**Fig. 74.2:** Herpetic Whitlow; (a) pre-acyclovir treatment, (b) post-acyclovir treatment.

a&b) and there is a good rationale for using acyclovir suppressive therapy to prevent HIV transmission.<sup>6</sup> Vidarabine, famciclovir, and valaciclovir are newer alternatives. Intravenous foscarnet is given for acyclovir-resistant HSV. Cidofovir gel and 5% imiquimod have been effective topical therapies for cutaneous herpetic infections, especially caused by acyclovir-resistant HSV strains.<sup>7,8</sup>

### Varicella Zoster Virus

Herpes zoster is seen in 6.9–25% of Indian population with HIV infection.<sup>9</sup> Occurrence of HZ due to reactivation of the virus is common in HIV patients and may be the first sign of immunosuppression. Since it is rare in normal children, HZ in young children should alert the physician to the possibility of HIV infection.

While in majority of the cases, the disease runs a typical course with a vesicular eruption in a dermatomal pattern, some cases develop severe hemorrhagic and necrotic lesions that may extend over several dermatomes, and eventually disseminate all over the body.<sup>10</sup> According to Leibovitz et al.,<sup>11</sup> chronic VZV infections associated with HIV-1 infection begin as vesicles and progress into necrotic, non-healing ulcers.

Disseminated herpes zoster is defined as involvement of more than three contiguous dermatomes, more than 20 lesions scattered outside the initial dermatome, or presence of systemic infection (hepatitis, pneumonitis, encephalitis).<sup>8</sup> Conjunctivitis or optic





(a)



(b)

**Fig. 74.3:** Giant herpes ulcer in a bed ridden patient; (a) pre-acyclovir treatment, (b) post-acyclovir treatment.

neuritis may complicate herpes zoster ophthalmicus, and patient should be referred to the ophthalmologist. Acute retention of urine, hemorrhagic cystitis, and constipation can occur due to involvement of sacral nerves.

Clinical diagnosis is supported by Tzanck smear and skin biopsy in cases with unusual presentations. Fluorescent antibody testing, viral culture, and PCR are done for confirmation of diagnosis.

Oral acyclovir 800 mg five times a day for 10 days is the treatment of choice.<sup>12</sup> It should be started preferably within 48–72 hours after the appearance of rash. However, in immunocompromised status, they may be treated even after 3 days of onset of the rash. Systemic parenteral therapy with acyclovir 10 mg/kg three times a day for 7–10 days is indicated especially when sight, sphincter function and facial expression are threatened, and where pulmonary or neurological involvement is suspected.<sup>13</sup> Vidarabine, intravenous foscarnet and recombinant IFN- $\alpha$  are possible alternatives for emerging acyclovir resistance.<sup>13</sup> Live attenuated (Oka/Merck Strain) VZV (Zoster Vaccine) may boost immunity and varicella immunoglobulins can prevent or modify the clinical illness.<sup>14</sup> An important component of management is the treatment of pain. Carbamazepine, amitriptyline, and

gabapentin are the options available. Intractable post-herpetic neuralgia has been occasionally treated with intrathecal administration of methyl prednisolone. A topical or systemic antibiotic is often needed for secondary infections.

### Epstein–Barr Virus

Oral hairy leukoplakia (OHL) is caused by the Epstein–Barr virus (EBV). It is considered as one of the first opportunistic infections occurring in approximately 15–20% of HIV-positive individuals.<sup>15</sup> Following the widespread use of highly active antiretroviral therapy in the mid 1990s in western countries, the prevalence of oral hairy leukoplakia has significantly declined. Patients with OHL generally have moderate to advanced immune suppression, with a median CD4 count of approximately 235 cells/ $\mu$ L.<sup>15</sup>

OHL has clear prognostic value for subsequent development of AIDS and it is classified as a CDC category B clinical marker of HIV disease. Typical OHL lesions are asymptomatic, raised, white, non-removable, corrugated hyperkeratotic lesions on oral mucosal surface. The lesions most often cluster on the lateral aspect of the tongue. The lesions can be unilateral or bilateral. OHL can look like thrush, another common problem characterized by white patches that occurs in HIV-positive patients. However, thrush usually comes off when it is lightly scraped with a toothbrush, whereas OHL does not.<sup>16</sup>

In most circumstances, the diagnosis of OHL is made on clinical findings. If a biopsy is performed, histologic features consist of nuclear changes (Cowdry type A inclusions, ground glass appearance, nuclear beading), profound acanthosis, lack of an inflammatory infiltrate, enlarged cells, regions of ballooning cells, and epithelial hyperplasia.

Fortunately, OHL does not usually require specific therapy.<sup>17</sup> Most patients experience resolution of OHL after taking potent antiretroviral therapy.

### Cytomegalovirus (CMV)

Reactivation of CMV in HIV infection occurs with a CD4 count below 50/ $\mu$ L. Skin involvement with CMV is relatively uncommon but when CMV affects the skin, the mortality is about 85% in 6 months.<sup>18</sup>

Ulcers in the perineal region are the most common presentation. HSV is proposed to be the initiating infection leading to ulcer formation, with CMV secondarily localizing in the granulation tissue. Non-specific maculopapular eruptions or papulovesicular, nodular, purpuric, and ulcerative lesions are observed. Diagnosing CMV infection in individuals infected with HIV is considered a poor prognostic sign.

Skin biopsy shows characteristic CMV inclusions and the material can be cultured with human fibroblasts to demonstrate the cytopathic effect.

Treatment and prophylaxis is based on immune reconstitution with ART, although severe cutaneous ulcerative eruptions have been reported after initiation of ART. Intravenous foscarnet, ganciclovir, and cidofovir are specific treatments for severe cases.

## Human Papillomavirus Infection (HPV)

HPV infection is common during the course of HIV disease. HIV-positive women with severe immunosuppression are five times more likely than the HIV-negative women to have lower genital tract neoplasia.<sup>19</sup> Symptomatic HPV infection is only tip of the iceberg. Asymptomatic shedding is much more common in women with HIV/AIDS. Incidence of HPV infection does not decrease with ART and restoration of immune function.<sup>8</sup>

Warts are seen in about 5–30% of patients with HIV.<sup>20</sup> The warts can be extensive, numerous, and resistant to therapy. HPV-5 can cause a pattern similar to epidermodysplasia verruciformis with extensive verruca plana and pityriasis versicolor like warts.<sup>8</sup> Precancerous lesions like squamous cell carcinoma *in situ* (SCCIS) can occur periungually. These tumors are aggressive and erode underlying periosteum and bone.

Anogenital warts (Condyloma acuminata): HPV-6 and HPV-11 are the most frequently found types in anogenital warts and HPV-16 and HPV-18 are associated with carcinoma *in situ* and high-grade dysplasia (Fig. 74.4).<sup>21</sup> HPV causes various grades of squamous intraepithelial lesion (SIL), and invasive squamous cell carcinoma over cervix, anus, perineum, vulva, penis, oropharynx, and nail, more commonly in HIV infected than in HIV non-infected individuals. Invasive cervical cancer is aggressive in nature and is an AIDS defining condition.<sup>22</sup> ART and restoration of immune function may not cause regression of these dysplasias.

Each and every HIV-positive woman should be screened with Pap smear, histopathology, and PCR because asymptomatic shedders carry high potential for spreading the virus. All HIV-infected individuals should be examined annually for HPV infections by direct examination with speculum and anoscope. Samples for Pap smear should be taken during examination and biopsy is performed on individuals with high-grade squamous intraepithelial lesion.



**Fig. 74.4:** Giant genital wart.

Periodic follow-up examination should be done in patients with external anogenital SIL. Extensive intraoral condylomata acuminata (buccal florid papillomatosis) presents as multiple large plaques that can transform to verrucous carcinoma.

Conventional treatment for common warts may fail. Topical imiquimod and cidofovir can be used and HAART can lead to decrease in size of warts. Anal in situ neoplasia (AIN) can be treated with topical imiquimod, podophyllotoxin, 80% trichloroacetic acid or liquid nitrogen. Minimal invasive squamous cell carcinoma (SCC) can be excised and invasive SCC is treated by radiotherapy and chemotherapy. Oral HPV can be treated successfully with 1–3% cidofovir solution.<sup>8</sup>

GARDASIL is a recombinant quadrivalent vaccine against HPV types 6, 11, 16, and 18 which are responsible for 70% of cervical cancers and 90% of genital warts. It is currently indicated for use in girls and young women 9 through 26 years of age, before initiation of sexual activity, for the prevention of cervical, vulval, and vaginal cancers and warts. In July 2009, WHO has approved another cervical cancer vaccine Cervarix. It protects against HPV 16 and 18. Cervarix is formulated with AS04, a proprietary adjuvant that boosts the immune system response to HPV strains for a longer period of time. Due to high cost, HPV vaccination in developing countries seems to be a distant dream.<sup>23</sup>

## Molluscum Contagiosum Virus (MCV)

The molluscum contagiosum is a DNA virus in the Poxviridae family. Before the advent of ART, MCV infections were detected in 10% of individuals with HIV disease and in 30% of those with CD4 counts less than 100 cells/ $\mu$ L.<sup>8</sup> The clinical course of molluscum contagiosum in the HIV-infected patients differs significantly from that in the normal host as immunodeficiency progresses. Characteristic lesions are umbilicated pearly white papules with one or more central dull hyperkeratotic pores. Among HIV-infected individuals, the lesions tend to be numerous and may be nodular (giant molluscum) and disfiguring and the lesions may be of unusual morphology and sizes (Fig. 74.5 a&b).<sup>24</sup> Such unusual forms include solitary, endophytic, aggregated, inflamed, and giant MCs. MCs mimicking sebaceous nevus of Jadassohn, ecthyma, and giant condylomata acuminata have been reported. Widespread lesions are common and highly characteristic of HIV disease, and must be differentiated from cryptococcal histoplasmosis and *Penicillium marneffei* cutaneous lesions.<sup>10</sup> Skin biopsy may be required.

Introduction of ART is very effective for treatment in addition to conventional methods like cryotherapy, electrodesiccation, gentle curettage, and topical tretinoin.<sup>24</sup> For resistant cases, topical imiquimod 5% and topical or intravenous cidofovir can be used.<sup>8</sup>

## Human T-cell Lymphotropic Virus Infections (HTLV)

In HIV-infected adults, an increased incidence of inflammatory dermatoses, including seborrheic dermatitis, psoriasis, and





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**Fig. 74.5:** Molluscum contagiosum: (a) genital, (b) extra genital.

prurigo, has been reported after infection with HTLV-1.<sup>8</sup>

### Hepatitis B (HBV) and Hepatitis C Viruses (HCV)

Hepatitis B (HBV) and HIV co-infection occurs commonly. The incidence of HBV infection was 16.9% among HIV-positive persons and 14.4% among control subjects ( $p < 0.46$ ). The prevalence of HCV seropositivity was 12.7% among HIV-positive persons and 10.0% among control subjects ( $p < 0.31$ ).<sup>5</sup> Infection with HIV not only increases the risk that a person will progress from acute infection

to chronic HBV infection, but can also accelerate the progression of liver disease, resulting in increased morbidity and mortality.

### Other Viral Infections

Parvovirus B19 can cause cutaneous vasculitis and a persistent papular-purpuric gloves and socks syndrome with anemia.<sup>4</sup>

### BACTERIAL INFECTIONS

*Staphylococcus aureus* is the most common bacterial pathogen causing cutaneous and systemic infections in HIV disease. High prevalence of skin diseases due to *S. aureus* may be explained by high nasal carriage rates for the organism ( $\geq 50\%$ ) and altered immune function in conjunction with an impaired cutaneous barrier.<sup>25</sup> Up to 83% of patients with AIDS suffer from *S. aureus* infection at some point during the course of the disease and it is more commonly seen in HIV-infected children.<sup>26</sup> Drug using behavior and high-risk sex are the common risk factors for skin and soft tissue infections with *S. aureus*.<sup>8</sup> The incidence of infection increases with increasing immunosuppression. Bullous impetigo, ecthyma, staphylococcal scalded skin syndrome (SSSS), folliculitis, furuncles, carbuncles, cellulitis, hidradenitis-like lesions, botryomycosis, and pyomyositis constitute the wide range of primary staphylococcal infections in HIV. Secondary infection occurs in atopic dermatitis, herpetic ulcers, Kaposi sarcoma, scabies, and intertrigo. The most common mode for hematogenous dissemination is intravenous catheter.<sup>8</sup> Diagnosis is established by culture from appropriate sites. Management is directed at the acute infection and treatment of underlying dermatoses. Methicillin-resistant *S. aureus* may pose problems. Recurrent infection can be prevented by eradication of nasal carriage of *S. aureus* with mupirocin ointment (bid for 5 days each month) and long-term prophylaxis with rifampicin.

*Pseudomonas aeruginosa* causes primary infection like ecthyma gangrenosum and panniculitis in advanced HIV disease.

**Bacillary angiomatosis (BA)** is the vascular proliferative response to infection with gram negative, cat scratch disease organism, *Bartonella henselae* and *Bartonella quintana*. It most commonly affects skin and subcutaneous tissue. It usually occurs in patients with CD4 count  $< 200/\mu\text{L}$ . A major challenge in diagnosis of cutaneous BA is diverse presentation of the lesions. Cutaneous lesions may take one of the following forms: (i) solitary or multiple red, purple, flesh-colored hemangioma-like papules; (ii) nodules, often covered with a fine tightly adherent scale, mainly seen in subcutaneous variety; (iii) large, friable, pedunculated or polypoid exophytic masses; or (iv) hyperpigmented, hyperkeratotic, indurated plaques, typically on extremities, often overlying osseous defects. (Fig. 74.6a). BA also may have the appearance of a cellulitic plaque. Lesions may develop ulceration, discharge, crusting, and may be tender, associated with regional lymphadenopathy.<sup>27</sup> Bone pains are frequent in the forearms or legs. Bartonella-related pseudomembranous angiomatous papillomatosis of the oral cavity has been





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**Fig. 74.6:** Bacillary angiomatosis: (a) pre-treatment, (b) post-treatment with erythromycin.

described.<sup>28,29</sup> Because extensive visceral lesions may occur, skin lesions of BA must be regarded as a marker of possible internal involvement. Symptoms resulting from visceral involvement, including abdominal pain, vomiting, jaundice (peliosis hepatis), tenesmus, bloody diarrhea (colonic bacillary angiomatosis); psychiatric symptoms and difficulty in breathing secondary to laryngeal obstruction may occur. Diagnosis is most often based on clinical features coupled with biopsies of lesions and appropriate staining (Warthin Starry silver staining). Erythromycin (500 mg four times a day) is drug of choice to be given for 3–4 weeks (Fig. 74.6b). Tetracyclines are the first alternative. A combination

of doxycycline (100 mg twice a day) plus rifampicin (300 mg bid) may be used in patients with severe disease. Clarithromycin, azithromycin, chloramphenicol, ciprofloxacin, trimethoprim sulfamethoxazole, rifampin, isoniazid, and gentamicin combined with either doxycycline or ciprofloxacin produce good clinical responses. Cryotherapy, electrodesiccation, curettage, and surgical excision of solitary cutaneous lesions can be useful as adjunctive therapy.<sup>30</sup> Prevention of bacillary angiomatosis associated with *B. henselae* infection involves avoidance of contact with cats, while for *B. quintana* infection it involves delousing procedures. Use of macrolides for *Mycobacterium avium-intracellulare* prophylaxis in patients infected with HIV is protective against bacillary angiomatosis. Prognosis of bacillary angiomatosis is excellent because antibiotics are curative in most patients. Pitfalls include failure to distinguish KS (potentially life threatening) from BA.<sup>30</sup>

**Cutaneous tuberculosis (TB)** accounts for 0.14% of all cases of tuberculosis.<sup>31,32</sup> Although TB is a common disease in HIV-infected patients, exclusive cutaneous presentation is not common. The clinical presentation is diverse including scrofula, scattered violaceous papules, keratotic papules, nodules, tuberculides, and palmar or plantar keratoderma. An uncommon form of TB, tuberculosis cutis miliaris acuta generalisata, has reemerged among HIV-infected patients in recent years.<sup>33</sup> The clinical appearance of the lesions is not always characteristic and culture positivity for *M. tuberculosis* is not always obtained because skin lesions are typically paucibacillary. Marfatia et al. reported a case of non-healing perianal ulcer in an HIV-positive patient, who was not responding to antibiotics and anti-herpetic therapy [Fig. 74.7].<sup>34</sup> On further investigation, a swab from the ulcer showed acid fast bacilli (bacillary index 2+) on Ziehl–Neelson (ZN) staining which confirmed the diagnosis of tuberculous ulcer. The ulcer healed completely with 6 months of anti-tubercular treatment.<sup>34</sup>



**Fig. 74.7:** Tubercular perianal ulcer.

Atypical mycobacterial skin disease is usually due to *Mycobacterium avium intracellulare*. It manifests as violaceous papules, nodules, and ulcers as part of disseminated infection in patients with CD4 count  $< 50/\mu\text{L}$ . Primary cutaneous *M. avium* complex infection manifesting as sporotrichosis like lesions was also described in a patient with AIDS. Skin lesions have also been reported with *M. chelonae*, *M. fortuitum*, *M. kansasii*, *M. haemophilum*, and *M. marinum*. *M. haemophilum* infection presents as violaceous draining nodules and superficial ulcers on extremities, trunk, head, and genitalia. *M. kansasii* produces acneiform papules and indurated crusted plaques. They are treated with macrolides and ethambutol.

## FUNGAL INFECTIONS

The importance of fungal infections among HIV-positive patients was recognized in the early days of AIDS epidemic. The spectrum of illness ranges from asymptomatic mucosal candidiasis to overwhelming disseminated infection and life-threatening meningitis.

### Candidiasis

Mucocutaneous candidiasis occurs in three forms in persons infected with HIV: oropharyngeal, esophageal, and vulvovaginal disease. Oropharyngeal candidiasis is the most frequent opportunistic fungal infection affecting more than 90% of HIV-positive patients at some point during the progression of their disease. Esophageal candidiasis is reported in approximately 10% of patients with AIDS and is capable of producing incapacitating illness, wasting syndrome, and malnutrition.

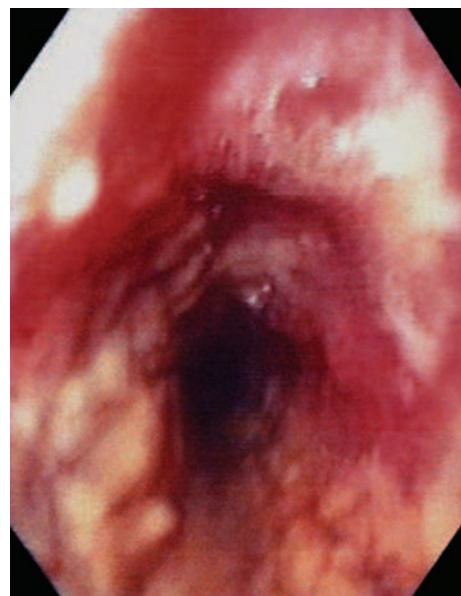
Most common cause of oropharyngeal candidiasis is *Candida albicans* in 77–100% patients. It is an imperfect diploid dimorphic fungus that resides as a commensal in gastrointestinal tract and mucosae. Others are infected with non-albicans species like *C. tropicalis*, *C. parapsilosis*, *C. guilliermondii*, *C. glabrata*, and *C. dubliniensis*. *C. dubliniensis* has been specifically associated with oropharyngeal candidiasis in HIV. Clinically, oropharyngeal candidiasis presents as pseudomembranous (thrush), atrophic (erythematous), hyperplastic forms and as angular cheilitis. Pseudomembranous candidiasis is most common. Thrush usually occurs with CD4 counts of  $< 300$  cells/ $\mu\text{L}$ . Symptoms of thrush are variable ranging from sore painful mouth, burning tongue, and dysphagia. It appears as cottage cheese like, creamy white exudative plaques on the tongue, which can be easily removed and leaves an inflammatory erythematous surface. Erythematous oral candidiasis presents as one or more flat, red, subtle lesions on the dorsal surface of the hard or the soft palate. The dorsum of the tongue may show loss of filiform papillae. Oropharyngeal cultures are not diagnostic as colonization is common. A KOH preparation will show pseudohyphae and budding yeast but are not mandatory for diagnosis. A presumptive diagnosis of oropharyngeal candidiasis can be made by visual detection of characteristic lesions (Fig. 74.8 a,b,c).



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\*e+

**Fig. 74.8:** Candidiasis (a) oral candidiasis with angular cheilitis, (b) cottage cheese like creamy white exudative plaques on the tongue, (c) esophageal candidiasis.



Esophageal candidiasis is an AIDS-defining condition, generally occurring in individuals with CD4 counts of  $<100$  cells/ $\mu\text{L}$ . It is usually accompanied by oropharyngeal candidiasis. Patients may complain of retrosternal burning sensation and odynophagia. In as many as 40% of patients with oropharyngeal candidiasis, esophageal involvement may be asymptomatic.<sup>35</sup> Persistent dysphagia even after disappearance of candidiasis after treatment warrants endoscopy to rule out other causes of esophagitis like cytomegalovirus, herpes simplex virus, tuberculous, and aphthous ulcers.

Uncomplicated vulvovaginal candidiasis affects 90% of HIV-infected women and occurs at higher CD4 counts than for other forms of candidiasis.<sup>36</sup> Recent studies indicate that candidal vaginitis, even if more frequent in HIV-infected women, is clinically similar to that experienced by HIV-negative women and does not appear to be of increased clinical severity.<sup>37</sup> Vulvovaginal candidiasis generally presents with marked itching, watery to curd-like discharge, vaginal erythema with adherent white discharge, dyspareunia, external dysuria, erythema, and swelling of labia and vulva with discrete pustulopapular peripheral lesions. The cervix usually appears normal. Symptoms typically exacerbate the week preceding menses with some relief once menstrual flow begins. A KOH preparation should be made to confirm the diagnosis.

Chronic fingernail candidal paronychia with secondary nail dystrophy (onychchia) is also common in HIV-infected children. Proximal nail fold inflammation is usually associated with proximal onycholysis or onychomycosis due to candida.

Milder episodes respond to topical therapy with nystatin, clotrimazole troches. Topical therapies are effective for uncomplicated oropharyngeal candidiasis; however, patients relapse more quickly than those treated with oral systemic antifungal therapy like ketoconazole, itraconazole or fluconazole.

Fluconazole is preferred over itraconazole or ketoconazole because its absorption is not dependent on gastric acidity or food intake, and patients are more likely to remain disease free during the fluconazole follow-up period. Fluconazole is recommended in a dose of 100–200 mg daily for 10–14 days. For maintenance therapy, 50–100 mg on alternate days is recommended for patients with less advanced disease or daily for patients with relapse or AIDS.

For vulvovaginal candidiasis, clotrimazole 1% cream or 5 g intravaginally for 7–14 days, or one 100 mg vaginal tab for 7 days is quite effective. Systemic therapy consists of fluconazole 150 mg as a single dose. Primary prophylaxis is not recommended due to cost, potential for development of resistance, drug interactions, and efficacy of therapy for acute disease.

## Dermatophytosis

Dermatophytosis in HIV patients is more varied, extensive, and atypical than in immunocompetent individuals. Most common is infection with *Trichophyton rubrum*. The lesions may be atypical with lack of active edge and central scaling (anergic form). They respond to topical and systemic anti-fungal therapy with imidazoles and triazoles. *Trichophyton rubrum* causes proximal

subungual onychomycosis, an infection of the undersurface of proximal nail plate. It is usually a sign of HIV disease and its diagnosis is an indication for HIV testing.

## Seborrheic Dermatitis

An increased colonization of *Malassezia furfur* has been reported in patients with HIV infection. Pityriasis versicolor and pityrosporum folliculitis arise from overgrowth of *M. furfur*. It is also thought to have a significant role in the pathogenesis of seborrheic dermatitis.<sup>38</sup> Seborrheic dermatitis (SD) is very common HIV-related opportunistic event and is usually a marker for early HIV disease (CD4 counts  $> 500$ ). Up to 85% of HIV-infected people experience seborrheic dermatitis at some time during the course of HIV infection. *Pityrosporum ovale*, a lipophilic yeast of the *Malassezia* genus, has also been implicated in the development of this condition. Clinically, it appears as erythema with yellow waxy scales most typically on scalp, around eyebrows, ears, and beard area but in HIV-positive individuals, rash also appears on chest, back, axilla, and groins.

Treatment includes topical application of mild-to-medium potency corticosteroids as well as topical anti-fungal creams such as the imidazole derivatives that have good activity against yeasts. For scalp, shampoos that contain coal tar, selenium sulfide, salicylic acid, and zinc pyrithione as well as ketoconazole are very effective.<sup>39</sup>

## Deep Fungal Infections

The commonly encountered ones are candidiasis, cryptococcosis, and histoplasmosis. Other fungal infections like coccidioidomycosis and *Penicilliosis marneffei* are seen usually in geographically restricted areas. *Penicilliosis marneffei* has been extensively reported in Thailand and South China, and more recently from North-East India. Coccidioidomycosis has never been reported in South-East Asia.

## Cryptococcosis

*Cryptococcus neoformans* is isolated in majority of AIDS patients because this variety is ubiquitous and predominantly affects immunocompromised hosts. It grows readily from soil contaminated with avian excreta, particularly those of pigeons. More than three fourths of the cases associated with AIDS develop this infection when the CD4 T-lymphocyte count falls below 50 cells/ $\mu\text{L}$ . CNS is the most common site of disseminated cryptococcal infection. Lung is most likely the portal of entry. Cutaneous cryptococcosis is a sign of dissemination present in approximately 10% of cases.<sup>40</sup>

The cutaneous lesions vary greatly in morphology and mimic many other dermatologic entities. They are usually characterized by multiple, discrete, flesh-to-red colored papules varying in size from 1 to 6 mm and often slightly umbilicated, resembling molluscum contagiosum. The lesions may appear as papules, tumors, vesicles, plaques, abscesses, cellulitis, purpura, draining



sinuses, ulcers, bullae, or subcutaneous swelling. It is often necessary to take biopsy and culture skin lesions resembling molluscum contagiosum to exclude the more serious condition of cryptococcosis.<sup>41</sup>

Cutaneous disease should be presumed to be disseminated and an appropriate workup for systemic involvement is essential. This includes a thorough history and physical examination, chest radiography or CT scanning to evaluate pulmonary involvement, lumbar puncture, and imaging of the CNS, and other studies as indicated. Primary cutaneous disease can be treated with oral fluconazole or itraconazole.

### Penicilliosis

It is an infection caused by *Penicillium marneffei*, a dimorphic fungus endemic to Southeast Asia and the southern part of China. Persons affected by penicilliosis usually have AIDS with low CD4 lymphocyte counts, typically <100 cells/ $\mu$ L. The most common presentation is a disseminated infection manifested by fever, skin lesions, anemia, generalized lymphadenopathy, and hepatomegaly. Lesions are present in approximately two thirds of cases and can be varied in appearance. Generalized papular eruptions, central umbilicated papules resembling those of molluscum contagiosum, acne-like lesions and folliculitis all may occur. Skin lesions commonly occur on the face, trunk, and extremities. Subcutaneous nodules can be occasionally seen. Diagnosis usually is made by identification of fungi from clinical specimens. Treatment with amphotericin B with or without flucytosine, or itraconazole, is the treatment of choice.

## PARASITIC INFECTIONS

### Scabies

Scabies can occur at any CD4 count, but the manifestations are more severe at lower CD4 counts.<sup>42</sup> In a study of 286 HIV-infected patients, scabies was seen in 4% of cases.<sup>43</sup> Not always as crusted (Norwegian) scabies, it can manifest in both typical and atypical forms. Although the classic, hyperkeratotic, papules, and plaques are most common, reported cases have ranged in spectrum from crusting with pruritus to a pruritic, papular dermatitis and those resembling Darier disease or psoriasis.<sup>44</sup> Nail thickening is typical in patients with crusted scabies.<sup>45</sup> Patients with Norwegian scabies can be infested with hundreds to thousands of adult female mites. This type of scabies is highly contagious and may spread rapidly through patients in an institutionalized setting.<sup>46</sup> When generalized papular, crusted, or eczematoid lesions are observed in HIV-positive patients, particularly with CD4 count less than 200/ $\mu$ L, scabies should be included in the differential diagnosis.<sup>47</sup>

Therapy requires the sequential use of scabicides, usually over a longer period than is required to clear an ordinary case of scabies. Compliance is a concern and the scabicides are best administered under supervision whenever possible. Isolating the index patient and treating the environment of patients with crusted or atypical

scabies is much more significant than in ordinary scabies. The transmission from an index patient with crusted scabies to other patients, healthcare workers, etc. is common.<sup>48</sup> Protective measures and early diagnosis and therapy are essential.<sup>48</sup>

### Leishmaniasis

*Leishmania* species can cause a wide spectrum of cutaneous lesions in HIV-positive patients ranging from localized cutaneous, mucosal, mucocutaneous, diffuse cutaneous, visceral or post-kala-azar dermal leishmaniasis (PKDL).<sup>49</sup> There is support for the suggestion that dissemination of lesions is more determined by host immunogenic status than by the virulence of the parasite species involved. Immune suppression caused by HIV infection is an important factor for atypical presentation and widespread progression of cutaneous leishmaniasis.<sup>50</sup> It also weakens response to classic treatment.<sup>51</sup>

In India, *Leishmania donovani* has been reported in PKDL associated with HIV. *Leishmania pifanoi* and *Leishmania infantum* have also been found in cutaneous leishmaniasis (CL) with HIV co-infection.<sup>50</sup> An HIV-infected patient has atypical and severe clinical presentation of CL in terms of sites and types of lesions (papulonodular) in relation to number of CD4 cells (>200).<sup>51</sup> Mucosal lesions of CL in an HIV patient should not be considered as mucocutaneous leishmaniasis (MCL) because parasites commonly disseminate and involve nasal and oral mucosa.<sup>52,53</sup> Diffuse (disseminated) cutaneous leishmaniasis with HIV co-infection is emerging as an extremely serious new disease. It has even been reported as the first manifestation leading to the diagnosis of HIV infection. In India, there is a high risk of mistaking diffuse cutaneous leishmaniasis especially for lepromatous leprosy since the latter is also endemic.<sup>51</sup>

There are two common therapies for leishmaniasis containing antimony (pentavalent antimonials), meglumine antimoniate and sodium stibogluconate.<sup>54</sup> HIV co-infected patients can be treated by various drugs like amphotericin-B, ketoconazole, miltefosine.<sup>55,56</sup> Protease inhibitors have been found to be active against leishmania species in two *in vitro* studies in Canada and India.<sup>57</sup> It is reported that ART therapy shows no difference in outcomes and relapses compared with those not on therapy.

### ICHTHYOSIFORM DERMATOSES

The spectrum of papulosquamous disorders in HIV patients encompasses xerosis, eczema, seborrheic dermatitis, psoriasis, and Reiter syndrome. In a study of 286 HIV-infected patients xerosis was found in 3%, eczema in 8%, and seborrheic dermatitis in 8%.<sup>43</sup> There are reports of chronic photodermatitis associated with HIV infection.<sup>58</sup> Cases of pityriasis rubra pilaris in the setting of HIV infection have been reported.<sup>59</sup>

HIV-infected patients commonly complain of increasing dryness of the skin (xerosis), which has been seen in up to 30% of patients.<sup>60</sup>

Severe intractable pruritus with eosinophilia may indicate a subset of HIV-infected patients with hyperactivation of humoral

immunity and augmented viral load.<sup>4</sup> Pruritus and xerosis are also the side effects of protease inhibitors.<sup>4</sup>

Typically, xerosis is most prominent on the anterior aspect of lower legs, but it may be quite widespread. Dry and thickened polygonal skin-colored scaling, as seen in acquired ichthyosis, is also seen in patients with advanced HIV disease. Thickening of the palms and soles may be present as well.<sup>61</sup> It becomes more severe with disease progression as CD4 counts decline.

Patients should apply mild topical steroid ointments (1.0–2.5% hydrocortisone or 0.025% triamcinolone) to the dermatitic areas three times a day and should cover all dry areas of the body with a moisturizing lotion or cream.<sup>61,62</sup>

## PSORIASIS

The prevalence of psoriasis in HIV-infected individuals is the same or slightly higher than seen in non-infected individuals, but its clinical presentation can be more florid, severe, and atypical.<sup>63,64</sup> Prevalence of psoriasis in HIV is 5–6%.<sup>65</sup> HIV-associated psoriasis appears paradoxical, being a T-cell-mediated disease in the face of decreasing T-cell counts. Furthermore, psoriasis is generally mediated by type-1 cytokines, whereas in HIV, type 2 cytokines tend to predominate.<sup>66</sup> Various theories for the worsening of psoriasis in HIV include immune dysregulation, an increase in viral and bacterial antigens in the skin, genetic susceptibility, and direct effects of HIV proteins on keratinocytes.<sup>67</sup>

Increase in the incidence of arthritis associated with psoriasis is seen as compared to the general population. Also, a higher frequency of guttate and inverse psoriasis as well as cases of generalized erythrodermic type of psoriasis have been reported in HIV-positive patients. Pruritus may be a serious problem for the HIV-infected patient with psoriasis. With scratching, secondary infection of excoriated psoriatic plaques with *S. aureus* may occur. Erythrodermic psoriasis in HIV-infected patients may be a sign of *S. aureus* septicemia and the psoriasis may improve dramatically with only intravenous antibiotics.<sup>61</sup>

The differential diagnosis of psoriasis include seborrheic dermatitis, atopic dermatitis, dermatophytosis, drug-induced eruption, and mycosis fungoides.<sup>4</sup>



**Fig. 74.9:** Extensive psoriasis in AIDS patient refractory to standard antipsoriatic treatment.

Psoriasis in HIV-positive patients is often refractory to standard anti-psoriatic treatment (Fig. 74.9).<sup>66</sup> HIV-positive patients who have either been started or restarted on ART show rapid improvement of psoriasis. Despite initial reports of enhanced HIV replication and immune suppression caused by UV light treatment, subsequent studies have not found the use of UVB or PUVA to accelerate HIV disease progression and have been used with variable success in the treatment of psoriasis. Systemic agents for psoriasis like methotrexate, azathioprine, and cyclosporine A, which cause non-specific or specific T-cell immunosuppression, should be avoided.<sup>68</sup> Cyclosporine and methotrexate have caused serious complications in HIV-infected patients such as leukopenia and fulminant Kaposi sarcoma.<sup>61</sup> Retinoids, especially etretinate, appear useful to help with moderate to severe psoriasis and do not cause immunosuppression.<sup>68</sup> Etanercept has been used with good effect in HIV-related psoriasis and arthritis in 1 patient but had to be discontinued because of the serious complications.<sup>4</sup>

## REITER SYNDROME

Classic Reiter syndrome (RS) is a parainfectious reaction associated with urogenital (*Chlamydia trachomatis*) or enteric infections (Shigella, Yersinia, Campylobacter, and Salmonella).<sup>68</sup> It consists of the triad of conjunctivitis, urethritis, and seronegative asymmetrical oligoarthritis. Whether the incidence of RS is increased in HIV infection, or whether HIV infection merely permits the expression or exacerbates the features of RS, is not known.<sup>69</sup> Immune dysfunction, cellular lymphokines, arthritogenic pathogens (Salmonella, Shigella, Yersinia, Campylobacter, and Giardia), and the direct effect of HIV have all been proposed as explanations. The increase in CD8 counts is believed to be important. Another hypothesis is that the HIV triggers an immune complex reaction. Finally, HIV may have direct effect on the synovial tissue. HIV-positive patients with RS also have a high incidence of HLA-B27 positivity.<sup>68</sup>

The classic cutaneous lesions of RS occur similarly in the HIV-associated RS as they occur in HIV-negative patients. They include hyperkeratotic areas over palms and soles known as keratoderma blennorrhagicum, circinate balanitis, conjunctivitis, which is generally transient and culture negative; urethritis/cervicitis; or diarrhea. The arthritis is inflammatory and usually affects one to five large joints of the lower extremities. Small joint involvement or axial arthritis is uncommon. Nails may show extensive subungual debris, may be horizontally ridged, and during severe flares, the nail plate may be so dystrophic as to appear absent. In the groin and axillae, red plaques identical to those seen in seborrheic dermatitis and psoriasis can be present.<sup>69</sup> Evanescent and often asymptomatic oral erosions may be present. Geographic tongue (i.e., showing migratory white patches) may also be found in patients with RS.

These patients may be treated with NSAIDs, sulfasalazine, or prednisolone. Etretinate, followed by RePUVA, proved to be the most effective systemic therapy, with only rare adverse effects.<sup>69</sup>

Treatment with cyclosporine A is moderately effective and not associated with progression of AIDS. There are reports of patients developing adverse effects such as *Pneumocystis jiroveci* pneumonia (PCP), Kaposi sarcoma (KS) on treatment with methotrexate.

## PRURITIC ERUPTIONS

Several chronically itchy papular and papulopustular eruptions, variously referred to as pruritic papular eruptions (PPE) of HIV infection, “itchy red bump disease,” papular urticaria, prurigo nodularis and insect bite reactions, have been reported in HIV-infected patients. PPE probably represents a heterogeneous spectrum of papular and papulopustular skin eruptions with similar or overlapping clinical and histological features and response to therapy.<sup>70</sup>

Pruritic eruptions can be classified as follicular, non-follicular, papular eruptions and others.

### Follicular Pruritic Eruptions

They can be eosinophilic folliculitis (EF), Demodex folliculitis, and Pityrosporum folliculitis.<sup>71</sup>

#### Eosinophilic Folliculitis

HIV-associated eosinophilic folliculitis is one of the variants of EF (eosinophilic pustular folliculitis or Ofuji disease). It is an idiopathic dermatitis that occurs in HIV-infected individuals with different clinical manifestations but with a distinctive histological feature characterized by predominantly eosinophilic infiltrate in the follicular infundibula.<sup>72</sup> The prevalence is uncertain, although one series reported it in 9% of HIV patients.<sup>73</sup> EF is more common in advanced HIV with CD4 <250/ $\mu$ L. Therefore, it identifies patients at immediate risk of developing opportunistic infections.<sup>4</sup> The cause is unknown but Th2 cytokines (IL-4, IL-5), RANTES, and eotaxin are increased in the lesional skin.<sup>74</sup> Foscarnet has also been implicated in development of eosinophilic folliculitis.<sup>75</sup>

Eosinophilic folliculitis (EF) presents as erythematous urticarial papules, pustules, and/or papules with pinpoint vesicles or perifollicular pustules on the face, neck, upper chest, and back, characteristically above the nipple line. The upper arms, eyelids, post-auricular areas, and scalp are often involved. It mimics staphylococcal or pityrosporum folliculitis, and acne vulgaris, with which it can co-exist.<sup>4</sup>

Pruritus is usually severe and unrelieved by anti-histamines, and tends to be chronic with occasional periods of remission. Laboratory examination may reveal elevated IgE levels and peripheral eosinophilia.<sup>70</sup>

Eosinophilic folliculitis frequently responds to UVB phototherapy and isotretinoin. There are reports that EF may also improve with cetirizine, itraconazole, metronidazole, and diaminodiphenyl sulfone. Ivermectin and long-term application of permethrin are used with some success implying a possible role for Demodex mites in the pathogenesis.<sup>72,74</sup>

#### Demodex Folliculitis

Mites such as *Demodex folliculorum* and *Demodex brevis* are natural hosts of the human pilosebaceous follicle and are ubiquitous obligatory ectoparasites of man. Most authors believe that the altered immune system favors the growth of this usually saprophytic agent so that it eventually causes a skin disorder. On the other hand, some authors suspect an unusual hypersensitivity against the mite itself.<sup>76</sup>

Demodex infestation can present as a mild form resembling pityriasis folliculorum and in some cases, rosacea-like lesions are seen.<sup>77</sup> The mild form presents as a pruritic papular eruption mainly limited to the face and neck.

Demodicidosis can be treated topically with 1% permethrin, 10% sulfur, 1% lindane, 5% benzoyl peroxide, 10% benzyl benzoate, or pilocarpine gel. Oral ivermectin and metronidazole can also be used.<sup>78</sup>

#### Pityrosporum Folliculitis (PF)

PF or malassezia folliculitis is caused by the invasion of the hair follicle by *Malassezia furfur*. Its development appears to have an immune component, and has been reported to occur mostly in immunosuppressed individuals. Moreover, the eosinophilic folliculitis seen in patients with HIV and AIDS may also be marked by colonization of the follicles with *Malassezia* yeasts.<sup>79</sup>

The classic presentation of PF is a follicular pattern of papulopustules arising in crops on the upper back, shoulders, chest, and sometimes on the scalp. The lesions are pruritic and they have a tendency to recur. Therapy must be directed both at restraining yeast overgrowth as well as tackling predisposing factors, to avoid recurrence.<sup>79</sup>

Specific treatment for *Malassezia* folliculitis comprises of oral azole antifungals in which itraconazole 200 mg PO once-daily  $\times$  4 weeks is preferred<sup>17</sup> and topical anti-fungal agents including 2% ketoconazole or ciclopirox creams or econazole foaming solution.<sup>79</sup>

### Non-follicular Eruptions

Non-follicular pruritic eruptions can be sub-classified into primary pruritic eruptions (viz. scabies, insect bites, transient acantholytic dermatoses, granuloma annulare, and prurigo nodularis) and eczematous eruptions (viz. atopic dermatitis, seborrheic dermatitis, nummular eczema, asteatotic eczema, photodermatitis, and drug eruptions).<sup>71</sup>

#### Pruritic Papular Eruption (PPE)

It is the most common cutaneous manifestation in HIV-infected patients. Anywhere between 18% and 46% of patients with HIV have this condition at sometime.<sup>80</sup> PPE can be regarded as a cutaneous marker of advanced HIV infection,<sup>81</sup> occurring at CD4 T-cell counts below 100–200/ $\mu$ L.





**Fig. 74.10:** Pruritic papular eruptions.

The etiology of this distressing condition is unclear, although an exaggerated response to an exogenous agent, such as arthropod bites, may underlie the pathogenesis. It is characterized by chronic pruritus and symmetric papular eruptions with excoriations on the trunk and extremities, with the absence of other definable causes of itching in an HIV-infected patient (Fig. 74.10). Patients frequently have prurigo nodules if the condition is long-standing. Lichenified patches and plaques on the arms and legs may be seen, probably representing an AIDS-associated, late-onset, atopic dermatitis.<sup>70</sup> PPE follows a chronic waxing and waning course, and may have an associated peripheral eosinophilia and elevated levels of IgE.<sup>70</sup> Identifying PPE's association with the immune dysregulation of HIV and distinguishing this condition from other pruritic disorders found in HIV-infected patients is important for optimal management.<sup>4</sup> Strictly it is diagnosis of exclusion.

Histopathologic examination in PPE reveals hyperkeratosis, acanthosis, focal dyskeratotic, and necrotic cells in the epidermis, and dermal fibrosis with proliferation of factor XIIIa-positive dermal dendrocytes. The dermal infiltrate also includes lymphocytes, plasma cells, eosinophils, and mast cells.<sup>4</sup>

Topical steroids, emollients, and oral antihistaminics should be the first line of management. Failing this phototherapy can be commenced. Several studies have shown that ultraviolet B (UVB) phototherapy is helpful for the treatment of HIV-associated pruritus.<sup>4</sup> The itching generally diminishes after 4–8 weeks of treatment. Pentoxifylline (usual dose recommended is 400mg three times daily for 8 weeks) and indomethacin have recently been reported to be effective in relieving HIV-related pruritus, although this has not been confirmed in randomized, controlled studies.<sup>70</sup>

## Pruritus in HIV

Patients with HIV infection commonly have elevated circulating IgE antibodies. Basophils have been shown to be hyper-releasable in HIV disease, and the mast cells in some patients are presumed to have a lower threshold for release of histamine, with attendant inflammatory reaction and pruritus. Patients with HIV disease

may also have direct neural infection with HIV leading to neural irritation and enhanced sensations of itching. Sometimes, autonomic dysfunction is associated with diminished sweating and sebaceous gland secretion that worsens xerosis and itching. In addition, patients infected with HIV may be under considerable stress, also leading to urticaria and itching. Finally, patients with HIV infection may develop pruritus secondary to underlying circulating pruritogens associated with different systemic disorders, such as chronic liver disease, chronic renal disease or lymphoma.<sup>82</sup>

## HYPERPIGMENTATION DUE TO HIV

Progressive pigmentation of the skin, nails, and mucosa is seen among HIV-positive patients. This can be attributed to opportunistic infections of the adrenal cortex culminating in Addison disease; or drug-induced hyperpigmentation due to zidovudine and antifungals like ketoconazole.<sup>70</sup> Alternatively, pigmentation may occur in HIV-seropositive patients who show no alterations in serum cortisone or ACTH levels and in whom drug-related etiology can be ruled out.<sup>71</sup> Rangnathan et al. studied 1700 HIV/AIDS patients, oral hyperpigmentation was seen in 24.6% cases. It was seen that patients with a CD4<sup>+</sup> <200/ $\mu$ L (54.7%) displayed pigmentation significantly ( $p < 0.05$ ) more often than those with a CD4<sup>+</sup> >200/ $\mu$ L (45.3%).<sup>72</sup>

In HIV disease, the immune system is dysregulated, leading to the elevation of interleukins (IL-1 and 6) and tumor necrosis factor- $\alpha$ , which leads to the release of  $\alpha$  melanocyte-stimulating hormone ( $\alpha$ -MSH) from the anterior pituitary. IL-1 upregulates  $\alpha$ -MSH receptor expression by melanocytes, and causes pigmentation.<sup>72</sup> It has been further suggested that cutaneous manifestations, including hyperpigmentation, might be a marker of immune suppression, since it was associated with a low CD4+ cell count.<sup>72,4</sup>

The hyperpigmented lesions due to HIV disease are diffuse, grey or brown, and generally multifocal.<sup>71</sup> Treatment with zidovudine (AZT) may result in hyperpigmentation of the nails, oral mucosa, and skin. The initial manifestation of hyperpigmentation is usually a bluish discoloration of the lunulae (proximal white portions) of the nails, most prominently on the thumb nails. This appears about 1 month after AZT therapy begins. Bilateral black pigmentation of the lateral mid-tongue has also been observed. The degree of hyperpigmentation of the nails and skin is related to dosage of AZT.

No melanocytic proliferation is evident on histopathological examination.

The lesions are asymptomatic and there is no specific treatment.<sup>71</sup> Cutaneous hyperpigmentation on the face may improve by avoiding sun exposure and using a sunscreen with SPF 15 or higher.<sup>73</sup>

## KAPOSI SARCOMA (KS)

Persons infected with HIV are at an increased risk for all cancers known or suspected to have an infectious cause, an effect believed

to be primarily mediated by lowered host immunity via the depletion of CD4<sup>+</sup> T cells.<sup>83</sup> Kaposi sarcoma (KS) and non-Hodgkin lymphoma were recognized as AIDS-defining illnesses early in the HIV epidemic. KS–AIDS has as aggressive course in HIV, especially among homosexuals, with an average age of 20–40 years.<sup>84</sup>

The incidence of Kaposi sarcoma has fallen markedly in the recent times, although its prevalence has not, Kaposi sarcoma originally accounted for as many as 35% of patients with AIDS, an incidence that has been declining with early detection of HIV infection.<sup>84</sup> Factors linked to KS include male gender, the HLA-DR5 genetic marker, abuse of nitrite drugs, exposure to semen or anal sex, or to several other viruses. HHV-8 is the most prominent of many viruses considered as a potential causal agent.<sup>85</sup> HHV-8 may be transmitted sexually, probably more by feco-oral route or the ejaculate rather than blood in HIV-positive homosexual men.<sup>4</sup>

Four different epidemiological forms of KS have been described that have identical histological features but developed in specific populations and have different sites of involvement and rates of progression.<sup>86</sup> HIV-related KS is known as epidemic KS.<sup>84</sup> Patients with AIDS-related KS can be divided into four groups: (i) those with no prior or co-existent opportunistic infection (OI), no systemic symptoms, CD4  $\geq 300$  cells/ $\mu$ L (median survival, 31 months); (ii) those with no prior or coexistent OI, no systemic symptoms, and CD4  $< 300$  cells/ $\mu$ L (median survival, 20 months); (iii) those with no prior or co-existent OI and presence of systemic symptoms (median survival, 15 months); and (iv) those with prior or co-existent OI (median survival, 7 months).<sup>87</sup> AIDS-related KS varies from minimal to fulminant disease.<sup>88</sup> It may be disseminated involving lymph nodes, viscera, and mucosa as well as skin.<sup>86</sup>

Cutaneous KS is multicentric and often involves the face, oral mucosa, palate, and genitalia.<sup>4</sup> Lesions may be multiple, follow skin creases, tend to be linear or to Koebnerize.<sup>4</sup>

Lymphedema may eventuate. The classical lesion is a purple patch, plaque or nodule, which may ulcerate (Fig. 74.11 a&b).<sup>4</sup>

The rate of progression varies from patient to patient and may not be related to the level of immunosuppression. Cutaneous involvement is the most common presentation (>90%). Other than the skin and oral mucosa, lungs (20%), gastrointestinal tract (40%) and lymph nodes are the sites commonly involved. Phimosis may occur if the lesion is located on the foreskin. Skin biopsy and immunohistochemical investigations are crucial to confirm the diagnosis of KS.<sup>84</sup>

Patients with KS–AIDS usually die from associated OIs or from gastrointestinal Kaposi sarcoma with hemorrhage. The mean survival rate of patients with KS–AIDS has been approximately 15–24 months, although the introduction of apparent immune system reconstitution using ART has extended survival substantially.<sup>89</sup>

The response of Kaposi sarcoma to ART is unpredictable, specific local or systemic therapy is often instituted as well.<sup>86</sup> In addition to ART, excellent treatments exist for both localized disease (topical gel, radiotherapy, and intralesional therapy) and advanced disease (liposomal anthracyclines, paclitaxel). Patients



\*c+



\*d+

**Fig. 74.11:** (a) Kaposi sarcoma; (b) Kaposi sarcoma with tinea corporis.

with Kaposi sarcoma who have widespread mucocutaneous disease, lymphedema, or visceral disease are usually treated with systemic cytotoxic therapy.

Novel therapies that have become available to treat AIDS-related KS include angiogenesis inhibitors and anti-viral agents.<sup>85</sup> Biologic agents such as interferon-alpha are now considered first-line therapy for some patients with epidemic cutaneous Kaposi sarcoma.<sup>86</sup>

There are reports of successful treatment with paclitaxel and anti-retrovirals.<sup>84</sup>

### ADVERSE CUTANEOUS DRUG REACTIONS (ADR)

The incidence of adverse cutaneous drug eruptions to a variety of drugs is high in individuals with untreated HIV disease (100 times more common than in the general population) and it increases with advancing immunodeficiency.<sup>90</sup> Although the clinical manifestations of drug eruptions are extremely diverse in nature, it is important to recognize these, as some of the eruptions can be serious. It is often not possible to specify the responsible drug or the pathogenetic mechanism on the basis of the clinical

appearance alone because the skin responds in a limited manner to a wide variety of stimuli.<sup>91</sup>

The urticarial papules and the eczematous cutaneous lesions that we have observed in AIDS patients, can be attributed to the mediators of the type I hypersensitivity reaction, characterized by the production of antibodies (mainly IgE) in response to the allergen. Sulfonamides, anti-convulsants, and anti-mycobacterial drugs are commonly used in patients with HIV disease. Patients with HIV have a much greater rate of ADRs to these drug classes, including severe and life-threatening hypersensitivity reactions. Between 50% and 60% of untreated HIV- infected individuals given intravenous TMP-SMX develop an exanthematous eruption (often associated with fever) 1–2 weeks after starting therapy, an incidence 10 times higher than that in general population.

The early detection and treatment of cutaneous adverse drug reactions, plus identification of the causative agent, are essential to prevent the progression of the reaction, preventing additional exposures and ensuring the use of alternative medications for the current condition.

In most of the cases, the implicated or suspected drug should be discontinued. In some instances, such as with morbilliform eruptions, the offending drug can be continued, and the eruption may slowly resolve. In cases of urticaria/angioedema or early Stevens–Johnson syndrome/toxic epidermal necrolysis the reaction can be life threatening and so the drug should be discontinued immediately.

### Cutaneous Adverse Drug Reactions (ADRs) due to Antiretrovirals (ARV)

Lifelong multidrug therapy is required for near complete suppression of HIV-1 replication, thereby exposing patients to the risk of ADRs and drug toxicities.

In a review of over 1000 patients in a Swiss cohort that received combination ARV therapy, 47% and 27% of the patients were reported to have clinical and laboratory adverse events, respectively.<sup>92</sup> Cutaneous manifestations of ADRs can serve as a surrogate marker of internal involvement. Antiretrovirals can lead to short-term toxicities or long-term side effects:

**A. Short-term toxicities:** SJ syndrome, hypersensitivity.

**B. Long-term side effects:** Morphologic complications:

- Lipoatrophy (facial and of extremities)
- Lipoaccumulation/lipohypertrophy
- Breast enlargement
- Dorso-ventral fat pad
- Lipomas
- Cosmetic disfigurement

### Hypersensitivity

Drug hypersensitivity typically manifests as erythematous maculopapular or morbilliform, pruritic and confluent rash with or without fever. Rash is most prominent on the body and arms and begins after 1–2 weeks of therapy. Constitutional features like

fever are often prominent and can precede rash (with abacavir) or occur without rash. Other principal features include myalgia, fatigue, and mucosal ulceration. Less common features (<5%) are SJ syndrome or toxic epidermal necrolysis (TEN) (0.3%), anicteric hepatitis, hypotension, acute interstitial nephritis, and acute interstitial pneumonitis.<sup>93</sup>

All NNRTI (Nevirapine, Delavirdine, Efavirenz), NRTI (Abacavir) and PI (Amprenavir) are common ARVs that cause hypersensitivity. Nevirapine (NVP) has been associated with a skin rash in 32–48% of patients,<sup>94</sup> with comparatively high incidence of rash in the Asians.

The most common symptomatic side effect of nevirapine is rash, usually occurring in the first 6 weeks of treatment.<sup>95</sup> Nevirapine-associated skin reactions usually are mild to moderate but in some cases are severe and life threatening, like extensive maculopapular rash, Steven–Johnson syndrome (Fig. 74.12) and toxic epidermal necrolysis.<sup>96</sup> Rash may also accompany hepatotoxicity. Patients with rash should be evaluated carefully for signs of severe skin reaction and for liver toxicity. In case of severe skin, liver, or hypersensitivity reaction, nevirapine must be discontinued permanently.<sup>95</sup>

It has been shown that the appearance of NVP-associated rash seems to depend on the levels of NVP and can be significantly reduced with a lead-in treatment period of 200 mg daily dose for the first 2 weeks, followed by 200 mg twice daily.<sup>97</sup>

Marfatia et al. reported that the most common ADRs due to ART were cutaneous (44.4%), with nail hyperpigmentation in 14.4% and rash in 13.3%. Rash was mainly observed with nevirapine-based regimen and in one case with efavirenz (EFV)-based regimen. Nail and oral hyperpigmentation was attributed to AZT.<sup>98</sup>

About 50% of ARV hypersensitivity resolves spontaneously despite continuation of antiretroviral therapy. Therapy should be stopped if there is mucosal involvement, blistering, exfoliation, clinically significant hepatic dysfunction (e.g., tender



**Fig. 74.12:** Nevirapine-induced Stevens–Johnson syndrome.



hepatomegaly, aminotransferase concentrations greater than five times the baseline), fever ( $>39^{\circ}\text{C}$ ) or intolerable pruritus.<sup>99</sup> Glucocorticoids are ineffective for the prevention of nevirapine hypersensitivity. Rechallenge is possible for mild to moderate NNRTI hypersensitivity but not for abacavir, since several deaths have been attributed to abacavir rechallenge.

### Lipodystrophy Syndrome

The overall prevalence of lipodystrophy syndrome is about 50% after 12–18 months of therapy.<sup>100</sup> Sharma et al. studied 42 cases on stavudine-based regimen and 22.9% cases were found to have lipodystrophy, making it the second most common ADR due to stavudine, the commonest being peripheral neuropathy (39.6%).<sup>101</sup>

Main clinical features are peripheral fat loss (presumed lipoatrophy with loss of buccal fat and thinning of extremities and buttocks) and central fat accumulation within abdomen (crix –belly or protease paunch), breasts (gynecomastia), over dorsocervical spine (buffalo hump), and other peripheral lipomatosis. In adult males, there is an overall fat loss although fat accumulation may predominate.

Lipodystrophy syndrome is commonly seen with use of protease inhibitors. Indinavir and saquinavir can cause gynecomastia in males.

Lipodystrophy should not be diagnosed if patient has had a recent severe illness associated with weight loss.

Risk factors for lipodystrophy are genetic factors, low body weight before therapy, raised C-peptides and triglyceride concentrations after about 1 year, use of dual PI combination ritonavir-saquinavir and use of nucleotide analogue, stavudine. Other cutaneous reactions of ARV are (Table 74.1).

### General Principles of Management

To avoid adverse drug reactions, start drugs with non-overlapping toxicities and which have small risk of interaction with existing therapy. Always consider clinical settings such as pregnancy or pediatric age group, injecting drug user, chronic hepatitis B or C, hemophilia, and post-exposure prophylaxis.

In case adverse reaction develops, dose reductions are not advised because of potential for drug resistance. In patients with good control of viral replication, if possible, immediately switch to drug with different toxicity profile, if the etiology is certain. In patients with uncontrolled viral replication, stop the responsible

drug and initiate a new agent with different toxicity profile; but if possible aim for a new regimen with improved anti-viral activity.

After the adverse reaction has subsided, rechallenge should be medically supervised; but is contraindicated with hypersensitivity to abacavir; or if there is mucosal involvement; or rashes are of grades 3–4. Desensitization is probably inappropriate because of potential for induction of viral resistance.

### HAIR

Hair loss is common in patients with HIV-1 infection. The causes include chronic HIV-1 infection itself and recurrent secondary infections, nutritional deficiencies, immunologic and endocrine dysregulation, and exposure to multiple drugs. Histopathological examination conducted on hair samples of HIV-positive patients in USA showed that all patients had telogen effluvium.<sup>102</sup>

Softening, sudden graying, and straightening of the scalp hair may be observed. Some authors have reported silky hair (the “straight hair sign”) as a sign of HIV infection. Its pathogenesis is not known but some have reported it as being a manifestation of mitochondrial abnormality.<sup>103</sup> Alopecia areata may be associated with HIV disease and may be inflammatory and permanent. The apoptotic follicular stem cell population in higher proportion may represent a hair cycle disturbance in patients with diffuse alopecia related to HIV-1 infection.<sup>16</sup> Alopecia universalis is also reported. Patchy alopecia is a common finding in HIV-positive children. Occasionally, alopecia may be a dermatological manifestation of seroconversion. Elongation of eyelashes may be seen in HIV-positive individuals.<sup>16</sup> Acquired trichomegaly may be an early marker of HIV infection.<sup>104</sup> Acquired eyelashes hypertrichosis (AEH) in AIDS patients closely resembles hypertrichosis in porphyria cutanea tarda (PCT).<sup>105</sup>

Strands of hair may be used to predict the effectiveness of ART. Levels of protease inhibitors like indinavir in small hair samples are the strongest independent predictor of virologic success in a diverse group of HIV-infected adults. Hair samples offer a simple but accurate test as to whether the virus is sensitive to ART or not and also check the patients’ compliance.<sup>106</sup> Alopecia universalis is reported in patients under ART. Generalized alopecia can occur in patients with HIV who are treated with indinavir, a protease inhibitor.<sup>16</sup> Zidovudine can cause hypertrichosis including of the eye lashes. Hair loss is also reported with lamivudine, didanosine, stavudine, lopinavir, and ritonavir. Hair regrowth is seen after discontinuation of lopinavir and ritonavir.<sup>107</sup> Colebunders and Vandenbraeene have described curly hair (with lipodystrophy) during ART.<sup>108</sup>

Alopecia universalis associated with Grave disease has been reported in immune restoration disease.<sup>109</sup>

### NAILS

Criber et al. reported that nearly 70% of HIV-infected individuals have nail changes.<sup>110</sup>

Longitudinal ridges and pallor of the nail beds are the general effects of the chronic illness. Patients with AIDS or AIDS-related complex may develop Beau lines (transverse ridges)

**Table 74.1** Cutaneous Reactions of ARVs

Cutaneous reactions	Drug
Hypertrichosis	Zidovudine
Alopecia	Indinavir, didanosine
Nail hyperpigmentation	Zidovudine
Acute generalized pustular dermatoses	Protease inhibitors
Paronychia with lateral nailfold pyogenic granuloma-like lesions	Indinavir, zidovudine, lamivudine
Leukocytoclastic vasculitis	Zidovudine, didanosine

following episodes of severe illness.<sup>111</sup> Half and half nails, loss of lunula, leukonychia, onycholysis, onychoschizia, periungual erythema, longitudinal melanonychia, linear melanosis, and onychodystrophies are also seen in HIV.

Nail dyschromia in patients infected with HIV was first described in 1987 by Furth and Kazakis.<sup>112</sup> Blue nails are a sign of HIV infection.<sup>4</sup> Yellow discoloration of the distal portion of some nails is a frequent finding in HIV-infected patients. Although originally described under the diagnosis of yellow nail syndrome (YNS), the yellow discoloration of the nails observed with HIV infection is a different condition. Typical nail changes of YNS such as reduced nail growth, nail plate over curvature, scleronychia and loss of cuticles are not observed. Color changes can be preceded by opacification and decreased size or loss of lunulae. Onycholysis at the distal part of the lateral nail folds as well as transverse/longitudinal ridging can be present. Great toe nails are most commonly involved while the fingernails are only rarely affected. Asymmetrical involvement of several nails is usual. Yellow toe nail changes have been considered together with seborrheic dermatitis, oral hairy leukoplakia, and oral candidiasis as possible indicators of progression to established AIDS.<sup>111</sup>

Digital clubbing has been reported in infants with AIDS; it can also occur in adults. Patients with clubbing are younger, have significantly higher digital index (the ratio of the nail bed: distal phalanx circumference) and have longer duration of HIV disease. HIV infection should be considered in the differential diagnosis of acquired digital clubbing.<sup>113</sup> Psoriatic onychia is more common than in patients of psoriasis in the general population. Clinically there is faster appearance of onycholysis.<sup>114</sup> Miralles et al. have proposed a new category of pityriasis rubra pilaris (type 6) in AIDS patients where all nails show paronychia, subungual hyperkeratosis, and hyperplastic cuticles.<sup>115</sup>

A lichenoid dermatitis associated with nail changes has been described in a 39 year old man with AIDS. Splinter hemorrhages and periungual lichenoid papules were also present.<sup>111</sup>

Kaposi sarcoma can involve nail area. A periungual Kaposi sarcoma resembling chronic paronychia has been reported in a patient with AIDS. Subungual squamous cell carcinoma has also been frequently reported in AIDS, often in association with HPV 16.<sup>111</sup>

Diffuse nail pigmentation as well as longitudinal or transverse hyperpigmented bands are frequently seen in HIV-positive patients receiving zidovudine (in 40% of the patients) (Fig. 74.13). Multiple longitudinal melanonychia as well as hyperpigmented macules on the palms, soles and mucous membranes unrelated to AZT (zidovudine) treatment have also been described in AIDS. The serum level of  $\alpha$ -MSH was significantly increased in 1 patient.<sup>111</sup> Zidovudine can also lead to paronychia or pyogenic granuloma. Paronychia and ingrown toe nail are particular complications of indinavir.<sup>4</sup>

## ORAL MUCOSA

Nearly all HIV infected, untreated individuals experience disorders of the oropharynx during the course of the disease. They



**Fig. 74.13:** Zidovudine (AZT)-induced longitudinal hyperpigmented band on thumb nail.

can be due to infectious (already discussed) or non-infectious causes. Oral ulcers are the presenting clinical manifestations in 10–20% of HIV-positive patients. The detection of oropharyngeal disorders may be an indication for HIV serotesting.<sup>8</sup> Principle dermatological manifestations of HIV seroconversion include oral ulcerations and oropharyngeal candidiasis. Others like transient intraoral redness, erosions, and xerostomia are also commonly found in early HIV infection and seroconversion.<sup>4</sup>

Idiopathic aphthous ulcers in HIV-infected individuals tend to be large (>1 mm in diameter) in contrast to minor recurrent ulcerations in immunocompetent populations. They are painful ulcerations of the oral mucosa, hypopharynx, and esophagus. In some cases, they may be very extensive; often involving the tongue, gingiva and the lips, and pain upon swallowing may be so severe that rapid weight loss ensues.<sup>10</sup> They are recurrent and refractory to treatment. Zalcitabine (ddC) causes aphthous-like ulceration of the oropharynx and esophagus.<sup>8</sup> Thalidomide has proved useful for these (idiopathic as well as ddC induced aphthous ulcers) at a dose of 100 mg nightly for 2 weeks followed by maintenance therapy of 100 mg every 5 days, with monitoring for peripheral neuropathy.<sup>4</sup>



**Fig. 74.14:** HIV: Linear erythema of gums.



Other oropharyngeal manifestations in HIV-infected individuals include xerostomia (10%), exfoliative cheilitis (9%), patchy depapillation of tongue (6%), oral manifestations of Reiter syndrome, petechiae from thrombocytopenia, hyperpigmentation, oral melanotic macules and ulcers of uncertain causes, and rarely linear erythema of gums<sup>8</sup> (Fig. 74.14).

Xerosis and cheilitis are common with protease inhibitors.<sup>4</sup> Indinavir can also cause cheilitis. Oral corticosteroid therapy for oral ulceration in HIV-infected individuals raises concerns regarding increased immunosuppression with exacerbations of OIs and neoplasms such as HSV infections and Kaposi sarcoma and oropharyngeal candidiasis.<sup>8</sup> Foscarnet and interferon are also responsible for oral ulcerations. Didanosine causes dysgeusia and xerostomia. Dysgeusia and perioral paraesthesia are caused by amprenavir and ritonavir.<sup>4</sup>

### IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

A subgroup of ART treated patients will exhibit paradoxical deterioration in their clinical status, despite satisfactory control of viral replication and improvement in CD4 counts. This clinical deterioration, known as the immune restoration syndrome or immune reconstitution inflammatory syndrome (IRIS), is a result of an exuberant inflammatory response towards subclinical, incubating opportunistic pathogens, or previously diagnosed, as well as response towards other as yet undefined pathogens/antigens.<sup>116</sup>

There are no specific laboratory markers to differentiate HIV IRIS from OIs. The appearance of OIs within a rather loosely defined period of 8–12 weeks after initiation of ART should be identified as IRIS.



**Fig. 74.15:** Herpes zoster occurring as IRIS.



\*c+



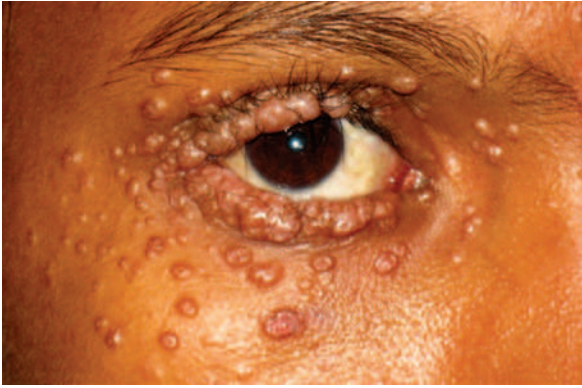
\*d+

**Fig. 74.16:** Hypertrophic lichen planus occurring after starting treatment with ART, at CD4 Count: 571/mm<sup>3</sup>; suggestive of IRIS; (a) lesions over legs; (b) lesions over hands and forearms.

The frequently occurring cutaneous IRIS events include herpes zoster (Fig. 74.15) and herpes simplex infections, MAC infection, Hansen disease, Kaposi sarcoma, Reiter syndrome, sarcoidosis<sup>117,118</sup> foreign body granulomas, acne vulgaris, dyshidrosis, and lichen planus (Fig. 74.16 a&b). There is emergence of tropical skin diseases, such as leishmaniasis and leprosy, presenting in the context of immune recovery.<sup>119</sup>

Thorough screening for hidden/OIs should be done before starting ART to prevent development of IRIS. Unless IRIS is life threatening, there is usually no reason to stop ART. There are no clear guidelines for the management of severe IRIS; approaches





**Fig. 74.17:** A 17-year-old HIV-positive male with numerous molluscum contagiosum lesions.



**Fig. 74.18:** Herpes zoster in an HIV-positive child.

include temporarily stopping the ART until the patient has stabilized and using systemic corticosteroid therapy to reduce inflammation.

### MUCOCUTANEOUS MANIFESTATIONS IN CHILDREN

Mucocutaneous diseases are more frequent in HIV/AIDS-infected children than in the normal population. Majority of these cutaneous disorders have an infectious etiology like severe, persistent, and recurrent infection with *Streptococcus pneumoniae* and *H. influenzae*, and their frequency is related to

the degree of deterioration of the immune system. Some diseases commonly observed in adults are rare in children; neoplasms are an exception.<sup>120</sup>

Mucocutaneous manifestations were noted in 53% of the patient population studied, the most common lesions were infectious in nature (fungal 67% with oral candidiasis as the most frequent fungal infection; viral 29%, mostly molluscum contagiosum (Fig. 74.17) and herpes zoster lesions (Fig. 74.18); parasitic 5% and bacterial 2%), followed by epidermal hyperproliferative states (29%), which included seborrheic dermatitis, ichthyosis, and xerosis. Hypersensitivity rashes accounted for 9%, three cases secondary to TMP/SMX and one presumed to be secondary to HIV. Recurrent aphthous ulcers of unknown etiology were noted in 2 children. All patients with CD4 less than 500/ $\mu$ L had mucocutaneous disease. There was an increase in incidence of molluscum contagiosum, recurrent herpes zoster and ichthyosis in the more immunosuppressed group. These patients had more severe or recurrent disease that was recalcitrant to therapy and had multiple manifestations.<sup>121</sup>

### Conclusion

It is well-quoted that skin is the mirror which reflects many internal conditions and this is aptly applicable to HIV infection/AIDS. Mucocutaneous manifestations of HIV have diagnostic and prognostic significance.

Pre- and post-ART era have seen an enormous change in the way HIV/AIDS interacts with skin. On one hand, ART has got tremendous impact on dermatologic manifestations of AIDS, with the duration and severity decreasing in post-ART years; ART on the other hand has come up with its own challenges, like ADR and IRIS. The initial manifestations of both ADR and IRIS can be dermatologic, providing a dermatologist the opportunity for early diagnosis and prompt management.

In many chronic dermatologic conditions, immune system plays a significant role and hence the change in immunity due to HIV infection alters the picture of all these conditions. HIV dermatology is an evolving science which needs inputs from physicians, dermatologists and all those working for HIV care. Interaction between skin and HIV/AIDS should be carefully studied and its thorough knowledge and a know-how of its implications are imperative for all HIV and skin care physicians, particularly in settings where resources are scarce and clinical diagnosis holds the fort.

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## Summary

- Dermatological diseases in HIV are a spectrum of inflammatory, infectious, and oncogenic disorders. They are in most of the situations diagnostic markers of HIV infection and opportunistic infections. They have specific prognostic significance independent of other markers.
- Langerhans cells in skin are CD4 bearing cells and their number as well as function is reduced in HIV. Moreover, being numerous in preputial skin, they are the prime targets of HIV.
- Mucocutaneous manifestations of HIV can be classified as infectious manifestations, non-infectious dermatoses, cutaneous adverse drug reactions (ADR) of ART, specific mucosal manifestations, hair manifestations, nail manifestations.
- Herpes simplex viral infection is one of the most common opportunistic infections in the HIV infected patients. HIV and HSV are co-transmitters of each other. HIV positive patients with HSV infection shed more HSV from genital mucosal tract even in absence of clinical herpes. HSV on the other hand perpetuates HIV disease progression. Herpes zoster presents atypically in a person infected with HIV where lesions can be hemorrhagic, crusted, and even disseminated (multi-dermatomal).
- Symptomatic HPV infection is only tip of the iceberg. Asymptomatic shedding is much more common in women with HIV/AIDS. Incidence of HPV infection does not decrease with ART and restoration of immune function. HPV causes various grades of squamous intraepithelial lesion, and invasive squamous cell carcinoma over cervix, anus, perineum, vulva, penis, oropharynx, and nail, more commonly in HIV infected than in HIV noninfected individuals. Invasive cervical cancer is aggressive in nature and is an AIDS defining condition.
- The clinical appearance of the lesions of cutaneous TB is not always characteristic and culture might be negative because skin lesions are typically paucibacillary. TB must always be suspected in a case of non-healing ulcer in an HIV positive patient, who is not responding to antibiotics and antiherpetic therapy.
- Oropharyngeal candidiasis is the most frequent opportunistic fungal infection in HIV positive patient.
- Pruritic papular eruptions are the most common cutaneous non-infectious manifestation of HIV. It is a marker of advanced HIV infection, occurring at CD4 T cell counts below 100–200/μL.
- Zidovudine is known to cause diffuse nail pigmentation as well as longitudinal or transverse hyperpigmented bands. All NNRTIs, especially nevirapine, can cause cutaneous ADR, which are mild to moderate in majority cases, but can be severe like SJS/TEN. Rash may also accompany hepatotoxicity. This might necessitate switch to efavirenz-based ART regimen. Protease inhibitors and stavudine can cause lipodystrophy syndrome leading to cosmetic disfigurement in AIDS patients.
- Paradoxical deterioration in the clinical status of HIV infected patients after initiation of ART, despite satisfactory control of viral replication and improvement in CD4 counts, can occur due to restoration of immune system and this phenomenon is known as **IRIS (immune reconstitution inflammatory syndrome)**. Thorough screening for hidden/opportunistic infections should be done before starting ART to prevent development of IRIS.

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# Pulmonary Manifestations of HIV Disease

Resham Vasani • Ratnakar Kamath • J.K. Maniar

# 75

## Introduction

The lungs, along with the gastrointestinal tract (GIT), constitute the first site of interaction between environmental pathogens and the human body. The lungs are the principal targets of HIV infection, and the pulmonary macrophages play an important role in the pathogenesis of the acquired immunodeficiency syndrome (AIDS). They are known to be discrete target cells for human immunodeficiency virus (HIV), and compelling evidence is accumulating that alveolar macrophages (AMs) from HIV-infected patients behave as versatile secretory cells that, acting as antigen-presenting cells, release a great variety of cytokines. The secretory products of AMs, pivotal to their immune effects, may contribute to localized immune dysregulation as well as to primary lung damage and clinical disease. Pulmonary macrophages are also thought to facilitate retroviral spread by their direct infection, by presenting HIV antigens to uninfected T cells, and by secreting cytokines that transactivate HIV expression. Therefore, persons with HIV infection are at an increased risk for a wide spectrum of opportunistic pneumonias, neoplasms, and pulmonary pathologies<sup>1</sup> (Table 75.1).

Pulmonary disease is a major cause of illness and death in adults with HIV infection. The presentation and type of pulmonary involvement varies with the stage of the disease, geographical area and patient's socioeconomic status. Primary HIV infection may involve the lungs in the form of pneumonitis. As the disease progresses, approximately 70% of the HIV infected patients will have at least one respiratory episode during the course of the disease. Table 75.2 gives a list of pulmonary conditions that are commonly seen in HIV according to the CD4 counts.<sup>2</sup>

## Infectious Complications

### BACTERIAL INFECTIONS

Upper respiratory tract infections such as otitis media and sinusitis occur with increased frequency in HIV patients. Bacterial tracheitis and recurrent bacterial bronchitis often associated

**Table 75.1:** Spectrum of Respiratory Tract Complications of Patients with HIV Infection

<b>Bacterial pneumonias</b>
<i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Pseudomonas aeruginosa</i> <i>Staphylococcus aureus</i> <i>Moraxella catarrhalis</i> <i>Rhodococcus equi</i> <i>Nocardia asteroides</i>
<b>Mycobacterial infections</b>
<i>M. tuberculosis</i> <i>M. avium</i> complex (MAC) Other nontuberculous mycobacteria
<b>Fungal infections</b>
<i>Pneumocystis jiroveci</i> <i>Cryptococcus neoformans</i> <i>Histoplasma capsulatum</i> <i>Aspergillus fumigatus</i> <i>Coccidioides immitis</i> <i>Blastomyces dermatitidis</i>
<b>Protozoal infections</b>
<i>Strongyloides stercoralis</i> (metazoa) <i>Toxoplasma gondii</i>
<b>Viral infections</b>
<i>Cytomegalovirus</i> (CMV) <i>Adenovirus</i> <i>Herpes simplex</i>
<b>Malignancies</b>
Kaposi sarcoma Non-Hodgkin lymphoma, including primary effusion lymphoma Carcinoma of the lung
<b>Other disorders</b>
Sinusitis Bronchitis Bronchiectasis Emphysema Lymphocytic interstitial pneumonia Nonspecific interstitial pneumonia Cryptogenic organizing pneumonia Pulmonary hypertension Immune reconstitution inflammatory syndrome



**Table 75.2:** Spectrum of Pulmonary Diseases in HIV Infected Individuals as per the CD4 Count

CD4 count	Disease condition
<500 cells/ $\mu$ L	<ul style="list-style-type: none"> <li>• Sinusitis/mastoiditis/otitis</li> <li>• Bronchitis</li> <li>• Bacterial pneumonia</li> <li>• Pulmonary tuberculosis</li> </ul>
<200 cells/ $\mu$ L	<ul style="list-style-type: none"> <li>• <i>Pneumocystis jiroveci</i> pneumonia</li> <li>• Kaposi sarcoma</li> <li>• Disseminated tuberculosis</li> </ul>
<100 cells/ $\mu$ L	<ul style="list-style-type: none"> <li>• Disseminated MAC</li> <li>• Cytomegalovirus disease</li> <li>• Disseminated fungal infection</li> </ul>

with bronchiectasis have also been reported in HIV infected individuals.

### Bacterial Pneumonias

The incidence of bacterial community acquired pneumonia (CAP) is increased in HIV-infected individuals because the depleted CD4 helper T cells lead to diminished humoral immunity. Hence, recurrent bacterial pneumonia is an AIDS defining condition.<sup>3</sup> Bacterial pneumonias may be the first manifestation of underlying HIV infection and thus presence of HIV infection should be considered in any patient presenting with bacterial pneumonias especially if the individual has no other risk factor for bacterial pneumonias or if pneumonia is nonresolving. Similar to persons without HIV infection, *Streptococcus pneumoniae* and *Haemophilus* species are the most frequently identified causes of bacterial CAP.<sup>4</sup> *Pseudomonas aeruginosa* and *Staphylococcus aureus* are also more frequently reported.

Risk factors for *Pseudomonas* include advanced HIV/AIDS (i.e., CD4 cell count at or below 50 cells/ $\mu$ L), underlying lung disease (bronchiectasis), neutropenia, corticosteroid therapy, and severe malnutrition. Risk factors for *S. aureus* include recent viral or influenza infection, use of injection/inhalational drugs, cigarette smoking, and previous *Pneumocystis jiroveci* pneumonia (PCP). Atypical pathogens such as *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* species are less frequent causes of pneumonia, and are encountered with similar frequency as among those without HIV.

*Rhodococcus equi* is a gram-positive, facultative, intracellular coccobacillus and is a cause of acute or insidious pulmonary infections (often cavitating pneumonia), bacteremia, and disseminated disease in patients with advanced HIV. Also, nocardiosis in AIDS is characterized by cavitary pulmonary infiltrates and brain abscess (Fig. 75.1).

### Clinical Presentation

The clinical presentation of HIV-associated bacterial pneumonia is similar to that in persons without HIV infection. They typically present with the acute onset (3–5 days) of fever, chills/rigors, chest

**Fig. 75.1:** Nocardiosis—Lung abscess.

pain, dyspnea, and productive cough with purulent sputum. Lung examination reveals evidence of consolidation and occasionally pleural effusion.

### Diagnosis

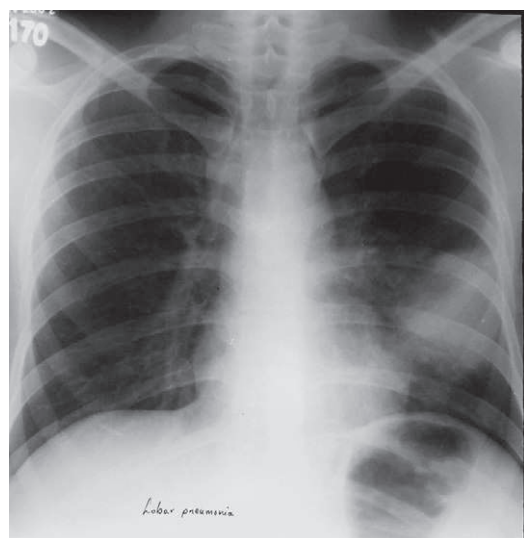
Laboratory testing is usually notable for an elevated white blood cell count, often with a predominance of polymorphonuclear leukocytes (PMNs).

The radiographic presentation is similar to usual CAP (Fig. 75.2a, b). Most persons with *S. pneumoniae* or *Haemophilus pneumoniae* present with unilateral, focal, segmental, or lobar consolidation, occasionally accompanied by pleural effusion. Focal airspace disease, ranging from patchy bronchopneumonia to segmental/lobar consolidation with air bronchograms may also be noted.

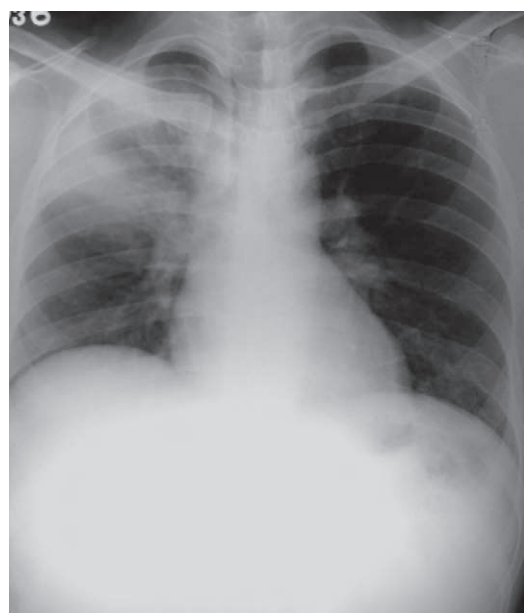
Diagnostic evaluation of suspected bacterial pneumonia includes a pretreatment expectorated sputum specimen for Gram stain and culture, two blood cultures, and thoracentesis if pleural effusion is present. Arterial blood gases typically reveal an increased alveolar-arterial (A-a) gradient. Since *R. equi* and *N. asteroides* are weakly acid fast, Ziehl–Neelsen staining should also be done to rule out these organism as well as *Mycobacterium tuberculosis*.

### Treatment

In patients with uncomplicated pneumonia without respiratory distress and normal oxygen saturation, treatment with amoxicillin-clavulanate and an additional second-generation cephalosporin should be instituted on an outpatient basis. Alternatively, a regimen consisting of macrolide, azalide, or tetracycline may be used. Seriously ill patients should receive a third or fourth-generation cephalosporin (e.g., ceftriaxone and cefepime, respectively) or a fluoroquinolone (e.g., levofloxacin). If *Legionella* is suspected, then the initial antibiotic should be clarithromycin, azithromycin, or a fluoroquinolone.



\*c+



\*d+

**Fig. 75.2 a,b:** Bacterial pneumonia.

### Prevention

Persons with HIV infection who have a CD4 cell count greater than 200 cells/ $\mu$ L should be given the 23-valent polysaccharide pneumococcal vaccine.<sup>5</sup> Since the duration of the protective effect of vaccination is unknown, revaccination every 5 years should be considered. Persons with a CD4 cell count less than 200 cells/ $\mu$ L can also be offered the vaccine. Although its efficacy may be lessened in those with advanced immunosuppression, observational studies suggest that the vaccine may still decrease the risk for pneumonia in this population.<sup>6,7</sup> If antiretroviral therapy is to be initiated, the vaccine can be given after the CD4 cell count rises above 200 cells/ $\mu$ L.

Other measures that may decrease the incidence of pneumonia among HIV-infected persons include the administration of the

inactivated influenza vaccine annually before influenza season. However, in a resource-limited setting, vaccination is not a feasible option. Trimethoprim-sulfamethoxazole (TMP-SMX), administered daily for PCP prophylaxis and azithromycin/clarithromycin administered for *Mycobacterium avium* complex prophylaxis can reduce the frequency of bacterial pneumonia. The efforts to improve smoking cessation could lead to substantial decreases in bacterial pneumonias.

### Tuberculosis

About one third of the world's population has latent tuberculosis. Most new cases occur in the most populated nations of India and China, but the highest rates of disease are seen in sub-Saharan Africa. *Mycobacterium tuberculosis* is the single most commonly seen coinfection among HIV infected persons in South and South-East Asia, especially India.<sup>8</sup>

HIV influences tuberculosis (TB) by causing the progressive loss of cell mediated immunity by reduction in the CD4 levels, impaired T cell proliferation, and reduced cytokine elaboration in response to mycobacterial antigen challenge. This enhances the risk of acquiring a new/active infection or reactivation of latent disease. Reinfection with a second distinct strain may also occur, in spite of completing the recommended treatment regimen.

Conversely, TB influences the HIV infection by activation of CD4 lymphocytes, which enhances their susceptibility to HIV. The cytokines elaborated by the lymphocytes and macrophages in patients with tuberculosis and HIV, in particular TNF- $\alpha$  and IL-1 upregulate HIV expression.

### Clinical Features

The diagnosis should be suspected not only in patients with pulmonary symptoms but also in those with constitutional symptoms like weight loss, fever of unknown origin and malaise. Tuberculosis can occur at any stage of HIV disease and at any CD4 cell count,<sup>9</sup> although the median CD4 cell counts range from 150 to 300 cells/ $\mu$ L.

In patients with higher CD4 counts ( $>300$  cells/ $\mu$ L) TB is more typically a reactivation disease, involving lungs predominantly with upper lobe infiltrates with or without cavitations and a positive Tuberculin test.<sup>10</sup> Symptoms include productive cough, fever, night sweats, weight loss, and occasionally pleuritic chest pain, hemoptysis, or dyspnea.

In patients with lower CD4 ( $<200$  cells/ $\mu$ L) counts, there is<sup>11</sup>:

- An increased likelihood of dissemination.
- Clinical features mimic *Pneumocystis jiroveci* pneumonia (PCP) with diffuse interstitial infiltrates or alveolar infiltrates.
- Extrapulmonary involvement of the central nervous system (CNS), the reticulo-endothelial system (RES) viz the liver, spleen, lymph node, bone marrow, and bone (vertebral bodies) is more common. Uncommon sites include the urinary tract, pericardium, skin, GIT, and the reproductive system.
- Atypical manifestations include primary progressive lung disease with acute or subacute fever, cough, breathlessness,

and decreased oxygen saturation accompanied by hilar lymphadenopathy and lower lobe, hilar, or interstitial infiltrates. This presentation is difficult to differentiate from other OIs and is mostly a new infection in a seriously immunosuppressed individual.

### Diagnosis

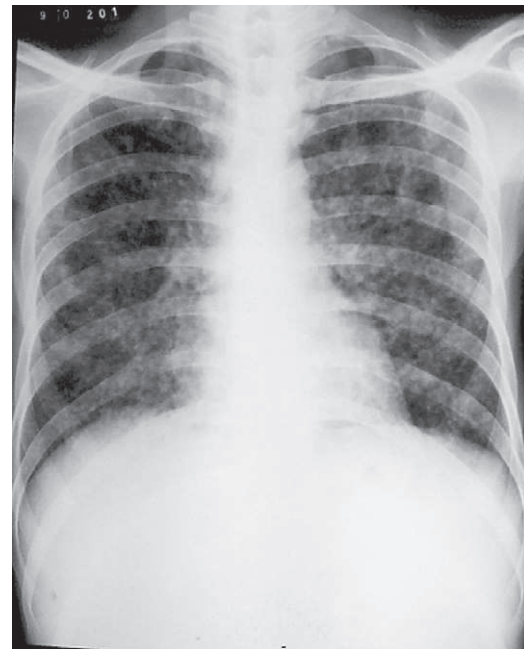
1. Acid fast smears of respiratory secretions or tissue samples are useful. Sensitivity of sputum AFB smear and culture in HIV infected patients is similar to the sensitivity in the overall population and depends on the degree of immunosuppression. However, only two-thirds to three-quarters of the HIV infected patients with pulmonary tuberculosis will have a positive AFB smear.

According to the WHO 2007 guidelines, pulmonary TB can be diagnosed if – one acid fast bacillus (AFB) is seen in at least one sputum sample.<sup>12</sup> Smear negative TB can be diagnosed if the following criteria are met:

- At least two sputum samples are negative for AFB.
- Radiographic abnormalities are consistent with active TB.
- Strong clinical evidence of TB.
- Decision by clinician to treat with full course of antituberculosis chemotherapy.

All patients diagnosed with smear negative pulmonary TB should have at least one sample sent for liquid media culture. A negative culture does not rule out TB but a positive culture confirms the diagnosis and conversion of the culture from positive to negative on follow-up suggests that the patient is responding to treatment.

2. Radiographic findings that suggest active HIV associated TB are:
  - Asymptomatic air space opacification.
  - Miliary or micronodular infiltrates (Fig. 75.3 a,b).
  - Cavitation which may be subtle (Fig. 75.4 a,b).
  - Pleural effusion (Fig. 75.5 a,b).
  - Mediastinal or hilar lymphadenopathy (Fig. 75.6).
  - Scattered soft pulmonary nodules (Fig. 75.7).
  - Increased cardiothoracic ratio suggestive of pericardial effusion.
  - Normal radiograph.
3. Molecular techniques include Roche Amplicor PCR and Gen-Probe Amplified PCR for *Mycobacterium tuberculosis*. Use of PCR is important in detecting the organism in areas like cerebrospinal fluid where it is not normally seen. Specimen for the test can be obtained by sputum collection, bronchoalveolar lavage, bone marrow aspirate and biopsy, fine needle aspiration cytology of the nodes and other sites.
4. Tuberculin skin test: The sensitivity of tuberculin skin test declines as CD4 counts fall. But even in advanced disease almost half of the patients with active tuberculosis will have a positive PPD. The test is however, done using 5 tuberculin unit (TU) and is considered positive when the induration is  $\geq 5$  mm. Among HIV infected patients with a



\*c+



\*d+

**Fig. 75.3a,b:** Miliary tuberculosis.

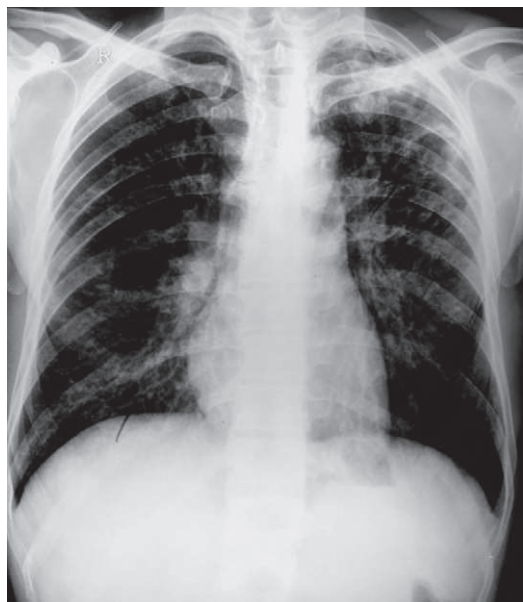
positive tuberculin test (PPD), the risk of developing active tuberculosis is 8–10% per year.<sup>13</sup>

### Treatment

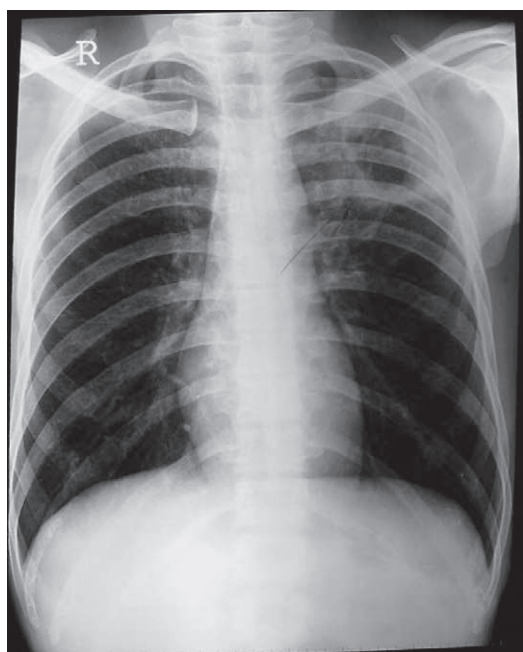
The therapy for drug susceptible tuberculosis is generally believed to be as effective in the HIV infected patient as it is in the general population.<sup>14,15</sup> Isoniazid (INH) or Rifampicin are the most powerful bactericidal drugs. Pyrazinamide is bactericidal against tubercle bacilli in an acidic environment in macrophages. Streptomycin is bactericidal against rapidly multiplying bacilli.

The induction phase of 2 months of Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol causes rapid killing of mycobacteria and decreases infectivity. The continuation phase of 4 months consisting of Isoniazid and Rifampicin causes sterilization and prevents relapses.





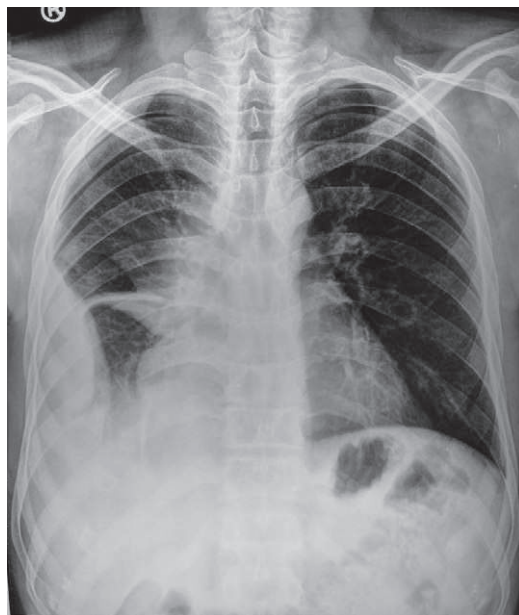
\*c+



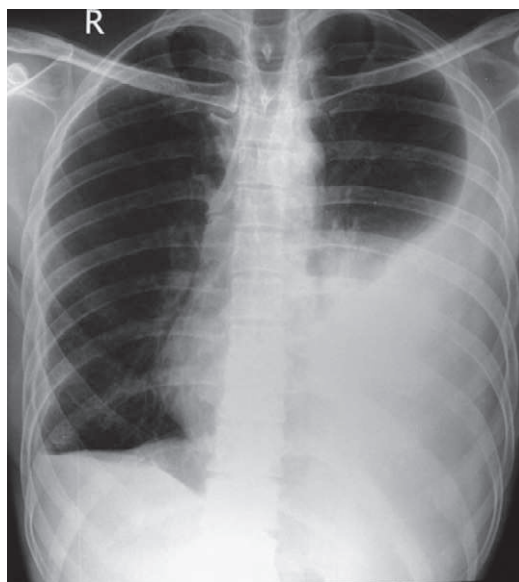
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**Fig. 75.4a,b:** Pulmonary tuberculosis with cavity.

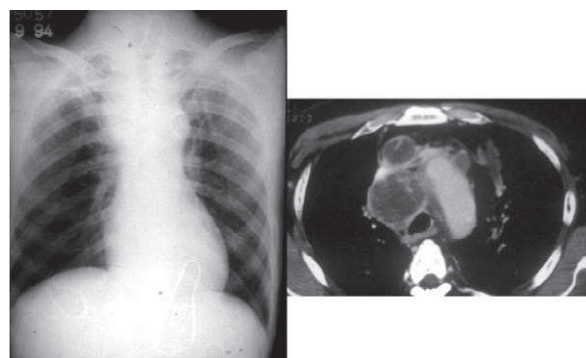
**Relationship between Antiretroviral Treatment (ART) and Antituberculosis Therapy (ATT)** Rifampicin based antituberculosis treatment can be given with NRTI and Efavirenz (EFV), but rifampicin interacts with protease inhibitors (PI) and nevirapine (NVP). Mortality is high in tuberculosis patients with low CD4 counts (<100 cells/mL) and consideration should be given to initiating ART as soon as antituberculosis drugs are tolerated (within 2 weeks).<sup>16</sup> If the CD4 counts are between 100 and 200 cell/mL, defer ART for the first 8 weeks of antituberculosis treatment. If the CD4 counts are between 200 and 350 cells/mL, defer ART until after completion of antituberculosis treatment.



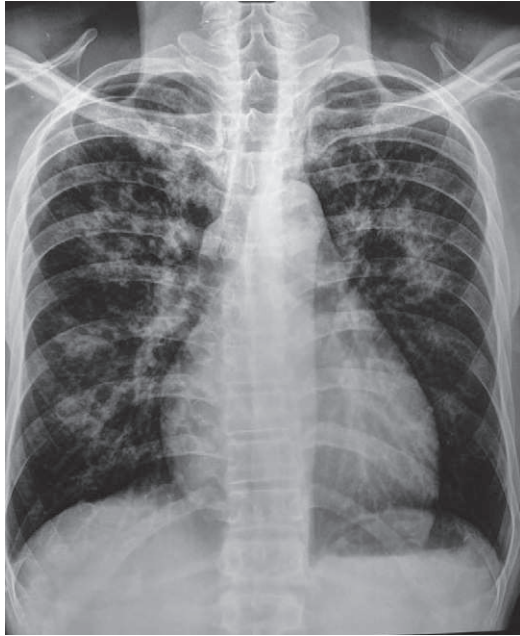
**Fig. 75.5a:** Encysted pleural effusion.



**Fig. 75.5b:** Pleural effusion due to tuberculosis.



**Fig. 75.6:** Mediastinal TB nodes.



**Fig. 75.7:** Pulmonary infiltrate in tuberculosis.

### Multidrug-Resistant Tuberculosis (MDR-TB)<sup>17</sup> and Extensively Drug-Resistant TB (XDR-TB)

MDR-TB is defined as resistance to at least rifampicin and isoniazid, while XDR-TB is defined as resistance to at least rifampicin and isoniazid of the first-line drugs, and resistance to any fluoroquinolones, and any one of the three injectable second-line drugs (capreomycin, kanamycin, amikacin). MDR and XDR tuberculosis commonly occur due to inadequate and/or inappropriate application of DOTS. Preventive measures include undertaking treatment of MDR and XDR tuberculosis only in select institutions with experience, expertise, and availability of required diagnostic and treatment facilities. The fluoroquinolones group of drugs are not recommended as first-line anti-TB drugs and their use should only be restricted to confirmed MDR-TB cases.

MDR tuberculosis should be suspected in:

- Retreatment patients who remain sputum smear positive after 3 months of intensive treatment.
- Retreatment failure and defaulter cases.
- Close contacts of MDR-TB cases.
- Chronic cases of TB.

The rate of cure of MDR tuberculosis is less than 50% in HIV negative patients. For this reason initial empirical treatment of AIDS patients with suspected MDR tuberculosis should be with first-line drugs (isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin) with or without fluoroquinolones depending upon the local patterns of resistance.

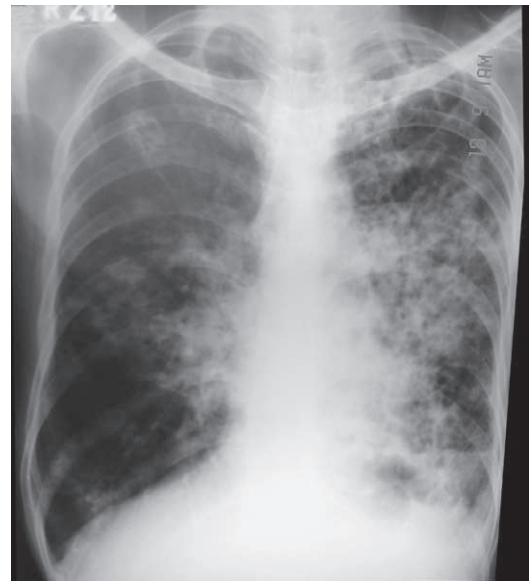
Treatment should include at least three drugs to which the organism is sensitive or not previously administered; and should be continued for at least 2 years or 12 months beyond sputum-culture conversion.<sup>13</sup> Sputum smears should be done

every month, while culture and X-rays should be repeated after 8 weeks when both microbiologic and radiographic improvement is evident (Fig. 75.8). If cultures are still positive after 2 months of treatment, isolation and drug sensitivity should be repeated and the treatment regimen re-evaluated.

Drugs used in the treatment of tuberculosis are enumerated in Table 75.3.<sup>11</sup>

### Prophylaxis of Tuberculosis<sup>10</sup>

WHO recommends giving preventive therapy to all HIV infected patients in countries with high TB burdens if



**Fig. 75.8:** Multidrug-resistant tuberculosis.

**Table 75.3:** Drugs Used in the Treatment of Tuberculosis

<b>First-line oral ATT</b>	Isoniazid Rifampicin Pyrazinamide Ethambutol
<b>Injectable antituberculosis agents</b>	Amikacin Kanamycin Capreomycin Viomycin
<b>Fluoroquinolones</b>	Ciprofloxacin Ofloxacin Levofloxacin Moxifloxacin Gatifloxacin
<b>Oral bacteriostatic second-line antituberculous agents</b>	Ethionamide Prothionamide Cycloserine Terizidone PAS Thiacetazone
<b>Antituberculous therapy with unclear efficacy (not recommended for routine use in MDR-TB)</b>	Clofazimine Amoxicillin-clavulanic acid Clarithromycin Linezolid





**Fig. 75.9:** Reactive Mantoux test—latent tuberculosis.

tuberculin skin testing cannot be done (Fig. 75.9). Isoniazid at a dose of 300 mg daily given for 12 months is the best studied regimen in HIV infection. Pyridoxine 25–50 mg daily should be prescribed to prevent INH induced peripheral neuropathy. A shorter regimen of 6 months has been rejected because of poor protective efficacy.

### **Mycobacterium Avium Complex (MAC) Disease**

This entity comprises *M. avium*, *M. InterCellulare*, and other poorly characterized strains not classified as either. It is one of the commonest OIs in the United States and other developed countries. These organisms are ubiquitous in the environment in both soil and water. Infection with this and other nontuberculous mycobacteria occurs when the CD4 count is  $0.1 \times 10^9/L$ .

Typically patients present with disseminated multiorgan involvement characterized by fever, night sweats, weight loss, fatigue, diarrhea, and abdominal pain. Laboratory abnormalities include severe anemia and abnormal liver function tests, especially raised alkaline phosphatase levels. Clinical findings include hepatomegaly, splenomegaly, and intra-abdominal lymphadenopathy. Less commonly, pneumonitis, pericarditis, osteomyelitis, skin and soft tissue abscesses, or CNS involvement is seen. Pulmonary disease without dissemination is uncommon in patients with HIV infection although rarely localized infection of lung is encountered with cavitating lung infiltrates.

The diagnosis is made by growth of MAC on culture of blood or involved tissue. A positive AFB smear is nonspecific without culture and species identification. The finding of two consecutive sputum samples positive for *Mycobacterium avium* complex (MAC) is highly suggestive of this infection. Cultures may take

2 weeks to be positive. The fastest technique with maximum yield for culture combines radiometric detection in liquid media with DNA probe identification.

The infection is resistant to first-line antituberculosis therapy and, like tuberculosis, requires combination therapy with at least three active drugs. Therapy consists of a macrolide usually clarithromycin (500 mg bid) or azithromycin (500 mg or 1 g daily) with ethambutol. Some elect to add a third from rifabutin/rifapentine, ciprofloxacin, or amikacin in patients with extensive disease. Therapy has to be continued life-long to prevent relapse unless potent ART is instituted. If CD4 T cell counts increase and sustain above 100 cells/ $\mu L$  after ART, discontinuation of therapy is possible after completion of 12 months. Primary prophylaxis for MAC is indicated in HIV infection and CD4 T cell counts less than 50 cells/ $\mu L$ .

## **FUNGAL INFECTIONS**

### **Pneumocystis Jiroveci Pneumonia (PCP)**

#### **Etiology**

*Pneumocystis jiroveci* (*Pneumocystis carinii*) considered as protozoan for long time has now been placed in fungal kingdom with proximity to ascomycetes based on phylogenetic analysis of rRNA sequences. This fungus predominantly occurs in two forms traditionally called as 'cystic form' (cysts) and 'trophic forms' (trophozoites). Cystic form (considered as sporangium) is thick-walled, measures about 5–8  $\mu m$  in diameter and contains daughter cells (spores/endospores), whereas the trophic form (considered as yeast) is small (2–5  $\mu m$ ), thin-walled and pleomorphic. The third, precyst form is now known as intermediate form.

#### **Susceptibility**

Since PCP has also been found to develop in nonimmunocompromised persons, the majority before the age of 13 years, it has led to the suggestion that PCP is caused by the reactivation of latent infection. The infection occurs once the patient's resistance is sufficiently impaired. In HIV patients CD4 counts of less than 200/ $\mu L$  considerably increase the risk of developing PCP.<sup>2</sup> The transient but profound fall in the CD4 T-cell counts in patients at the initial or primary stage of seroconversion may also result in PCP.

#### **Pathophysiology**

The *P. jiroveci* trophozoites bind to the alveolar epithelial cells leading to the destruction of the type 1 and subsequent proliferation of type 2 pneumocytes.<sup>2</sup> This leads to the disruption of the epithelial barrier leading to the increased capillary membrane permeability and hence the accumulation of foamy, proteinaceous eosinophilic exudate containing cellular debris, surfactant, and cysts of *P. jiroveci* in the alveolar space; along with inflammatory infiltrate in the interstitium. The increased phospholipase activity leads to the degradation of the surfactant. These events cause the physiological shunting and decreased lung compliance precipitating hypoxia.



### Clinical Features

The presentation is subacute over 2–4 weeks, with the common clinical features including night sweats, low grade fever, dry cough, and dyspnea that progresses from mild breathlessness on physical exertion to tachypnea at rest. Weight loss and retrosternal chest pain are rarely encountered. One third of the patients may present with sputum production and chest pain.

Physical examination of the chest is unremarkable in approximately 50% of the patients. Inspiratory crackles are the most common abnormal finding on lung examination. Typically the patient appears disproportionately symptomatic and distressed, when compared with the clinical signs and examination findings.

The severity of disease is classified based on the room air arterial blood gas (ABG) and difference between alveolar to arterial oxygen pressures ( $D_{A-a}O_2$ ). The clinical significance of this classification is to define the management plan depending upon the severity. Mild disease is defined as a  $PO_2 > 70$  mmHg and a  $D_{A-a}O_2 < 35$  mmHg while the severe disease has a  $D_{A-a}O_2 > 45$  mmHg. The severity worsens when the  $PO_2$  decreases and  $D_{A-a}O_2$  increases with progressive disease.

### Investigations

Sometimes the diagnosis of PCP becomes so obvious on clinical presentation and examination that treatment may be started empirically. There is evidence that such an empirical approach is not associated with any worse outcome.

### Diagnosis

Diagnosis requires demonstration of the organism in tissue or secretions.

**Microbiological Investigations** Induced sputum analysis, using 3% saline, has been claimed to be very sensitive (up to 90%) by some groups, but its usefulness is highly dependent on procedures being meticulously followed from bedside to laboratory. Sputum for *P. jiroveci* can be examined by doing a direct immunofluorescence (IF) test which employs anti *P. jiroveci* antibodies resulting in significantly improved sensitivity compared with standard staining methods. If sputum induction and examination is negative, then the patient should undergo fiber-optic bronchoscopy (FOB) and bronchoalveolar lavage (BAL). This procedure is more sensitive when performed in both the right upper lobe (RUL) and right middle lobe (RML). If BAL is also negative, then PCP is very unlikely and a lung biopsy obtained through transbronchial, thoracoscopic, or open technique is required to confirm or refute the diagnosis. Examination of induced sputum and even BAL may be negative if the patient has used pentamidine prophylaxis.

Other staining methods used to visualize the cysts or trophozoites of *P. jiroveci* include:

- Silver methenamine.

- Modified Giemsa
- Toluidine blue

Polymerase chain reaction (PCR) can be used to detect DNA in specimens such as induced sputum or BAL fluid.

**Radiological Tests** Chest radiographs: Patients with early PCP may sometimes develop mild symptoms before the appearance of any definite chest radiographic abnormality. Hence, a normal chest film does not rule out PCP. The most typical early abnormality found in PCP is that of bilateral, hazy, ground glass, perihilar infiltrates with sparing of the lung peripheries. The most common pattern in established disease is bilateral diffuse interstitial infiltrates. As the disease progresses, more homogenous consolidation with air bronchograms may develop. Ultimately the lungs may become massively consolidated and seemingly airless (Fig. 75.10).

Less common X-ray findings are<sup>18,19</sup>:

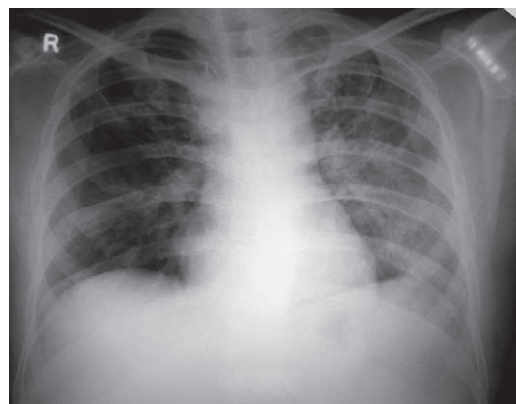
- Focal infiltrates.
- Nodular appearances with cavitation. Selective upper lobe involvement that may mimic mycobacterial disease.
- Subpleural cyst disease sometimes leading to spontaneous pneumothorax.
- Hilar lymphadenopathy.
- Pleural effusion and changes consistent with bronchiectasis.

High resolution computed tomography (HRCT) is useful in excluding PCP when history is suspicious but the chest radiograph remains normal. Such scans show bilateral ground glass opacification sometimes sparing subpleural lung tissue. (Fig. 75.11).

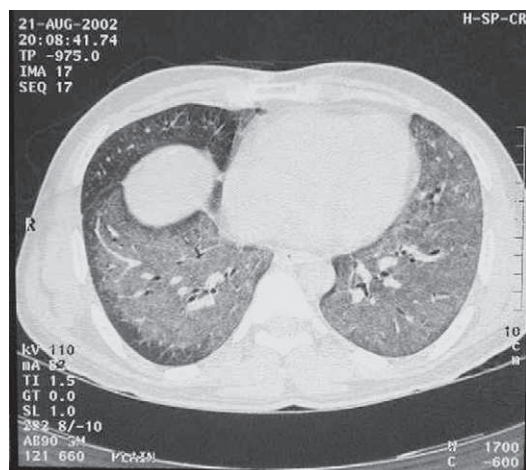
If radiography is inconclusive but clinical suspicion is strong, then a gallium scan can be performed. A diffuse uptake is consistent with PCP.

**Nonmicrobiological Investigations** Non-microbiological investigations include the following:

- CD4 T-cell count – invariably less than 200 cells/ $\mu$ L.
- Serum lactate dehydrogenase is increased in approximately 93% patients, specifically the LDH-3 fraction.<sup>20</sup> A serum LDH > 450 IU/L is strongly predictive and prognostic in PCP.



**Fig. 75.10:** Ground glass appearance—*Pneumocystis jiroveci* pneumonia.



**Fig. 75.11:** Ground glass appearance—*Pneumocystis jirovecii* pneumonia (high resolution computerized tomography scan).

- Decreased diffusion capacity of the lung for carbon monoxide (DLCO).<sup>21</sup>
- Monitoring of oxygen saturation by pulse oximetry. This is also used to screen patients with normal or minimally abnormal chest radiographs and resting saturations, in which case a failure to desaturate with exercise effectively rules out PCP.
- Anemia as a result of underlying disease or as a result of the treatment.
- Total leukocyte count may be normal or low.
- Hypoalbuminemia is not uncommon.

### Treatment

Mild disease may be treated on an outpatient (OPD) basis, but patients with moderate/severe disease should be hospitalized and treated. Adjunctive steroid therapy should be considered in addition to oxygen supplementation in patients with poor gas exchange. A transient worsening of symptoms is expected in all patients after initiation of treatment. Therapy is generally continued for 3 weeks. In mild disease, it may be discontinued after 2 weeks, but prophylaxis for recurrence is mandatory and should be instituted in all patients after completion of active treatment. The treatment is summarized in Table 75.4.

**Adjunctive Corticosteroids** High-dose corticosteroids given as adjuvant to conventional antimicrobial treatment in patients with moderate to severe PCP can be expected to significantly reduce the chances of deterioration and death.<sup>22</sup> The regimen is 40 mg bid for 5 days, then 20 mg bid for 5 days, then 20 mg once daily till therapy is complete.

Monitoring the response to treatment is extremely important, OPD follow-up is recommended twice a week. Both the patient's clinical improvement and compliance should be recorded. In moderate/severe disease, repeat ABGs should be performed to assess oxygenation status. An early transient deterioration in oxygen saturation is expected in approximately 50% of the treated patients. It improves by the end of the first week or with steroid therapy. In case the deterioration persists after 7 days, therapeutic failure should be considered and second line of drug therapy should be started.

**Table 75.4:** Treatment of *Pneumocystis jirovecii* Pneumonia

Treatment	Drug	Dose/route	Comments	Side effects
First line	Co-trimoxazole (Trimethoprim sulfamethoxazole)	15/75 mg/kg/d IV or oral	Any grade of pneumonia. Inexpensive, readily available. Acts also against other pathogens	Rash GI intolerance Bone marrow toxicity Avoid in G6PD deficiency
Second line	Pentamidine isethionate	4 mg/kg/d slow IV infusion	Severe PCP	Hypotension Hypoglycemia Nephrotoxicity Hepatotoxicity Pancreatitis Arrhythmias
Second line	Dapsone Trimethoprim	Dapsone 100 mg (oral) & Trimethoprim 300 mg (oral)	Mild to moderate PCP	Bone marrow toxicity Rash GI disturbances
Third line	Clindamycin Primaquine	Clindamycin 450–600 mg 3x/d (oral) & Primaquine 15 mg/d or 30 mg base (oral)	Mild to moderate PCP	Maculopapular rash <i>C. difficile</i> diarrhea Avoid in G6PD deficiency
Fourth line	Atovaquone	750 mg 2x/d	Mild to moderate PCP	Rash GI intolerance Poor enteric absorption
Fourth line	Trimetrexate with Leucovorin	IV Trimetrexate 45 mg/m <sup>2</sup> once daily; IV or oral calcium folinate 20 mg/m <sup>2</sup> four times daily. The dose may be doubled to 40 mg/m <sup>2</sup> if toxicity occurs. Leucovorin should be continued for 3 days after trimetrexate is discontinued	Mild to moderate PCP	Thrombocytopenia Neutropenia Oral and GI ulceration Hepatic and renal dysfunction Peripheral neuropathy

**Treatment for Respiratory Failure** Respiratory failure may develop despite adequate treatment and is treated along the usual lines with same indications for mechanical ventilation as for any respiratory failure. Adverse reactions to drugs occur in 50–100% of HIV infected patients. If an allergic reaction is moderate/severe or the patient cannot tolerate other effective medications to *Pneumocystis jiroveci* pneumonia, desensitization to trimethoprim-sulfamethoxazole is recommended.<sup>23,24</sup>

### Prophylaxis against *Pneumocystis Jiroveci* Pneumonia

Primary prophylaxis is administered to prevent pneumonia in predisposed individuals, while secondary prophylaxis given to prevent relapse after successful treatment.

Current recommendations for prophylaxis include<sup>25</sup>:

- Patients with CD4 count less than 200 cells/ $\mu$ L are 9 times more likely to develop PCP within 6 months than individuals on therapy.
- CD4/TLC ratio is less than 1:5.
- Oropharyngeal thrush or unexplained fever for 2 or more weeks even if the cells exceed the value of above.
- AIDS defining diagnosis such as Kaposi sarcoma, cerebral toxoplasmosis, or cryptococcal meningitis.
- Recovery from previous episode of PCP.

Drugs used in prophylaxis of *Pneumocystis jiroveci* pneumonia are enumerated in Table 75.5.

### Other Fungal Infections

Other fungal infections include cryptococcosis, histoplasmosis, blastomycosis, aspergillosis, sporotrichosis, penicilliosis, and coccidioidomycosis.

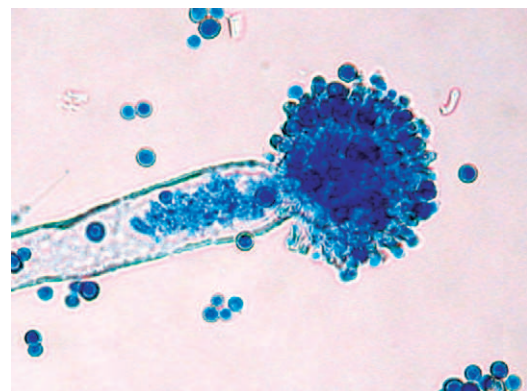
**Table 75.5:** Drugs Used in Prophylaxis of *Pneumocystis jiroveci* Pneumonia

Prophylaxis	Drug	Dosage	Side effects
First line	Co-trimoxazole 80/400 mg	2 tablets/d	Rash GI intolerance Bone marrow toxicity
Alternatives	Co-trimoxazole 80/400 mg Co-trimoxazole 80/400 mg	2 tablets 3x/wk 1 tablet/d	
Second line	Dapsone	100 mg/d	Rash GIT disturbance Hemolytic anemia in G6PD deficiency.
Third line	Atovaquone	750 mg 2x/d	Rash Deranged liver function
Fourth line	Nebulized pentamidine	300 mg/mo via jet nebulizer	Bronchospasm Metallic taste Renal impairment Hypoglycemia Pancreatitis

Cryptococcal pneumonia usually presents as a part of a disseminated infection with meningitis and fungemia. Pulmonary involvement occurs in a third, however, primary lung disease is rare. Pleurisy is the common presentation (40%). Chest radiograph patterns include large nodules, nonconfluent opacification, diffuse interstitial infiltrates, and cavitation. Enlarged nodes or pleural effusions are uncommon. Diagnosis includes the demonstration of cryptococcal antigen in serum which has more than 90% sensitivity and specificity for the presence of disseminated disease in AIDS patients. The disadvantage of this test is that it is not specific for site of involvement. Definitive diagnosis requires isolation of the organism from a respiratory source (BAL, sputum, lung tissue, or pleural fluid). Amphotericin B (alone or in combination with flucytosine) is the drug of choice. A total dose of at least 2–2.5 g of amphotericin B has to be administered before starting maintenance treatment. Patients with isolated pulmonary disease may be given 400 mg of fluconazole daily for life.

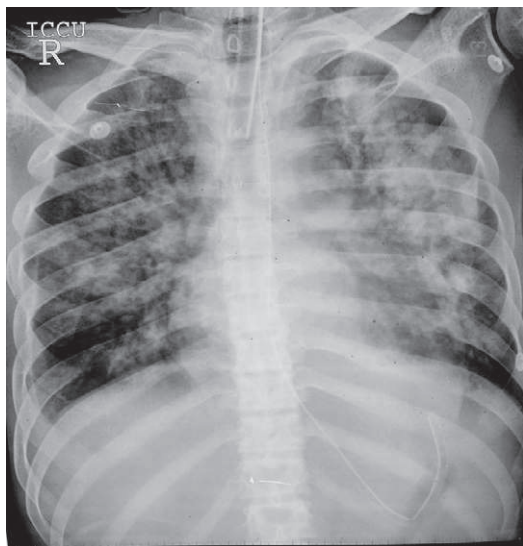
Invasive aspergillosis is not an AIDS-defining illness and is generally not seen in patients with AIDS in the absence of neutropenia or administration of glucocorticoids. The pulmonary disease may be parenchymal in the form of cavitary predominantly upper lobe disease or focal bilateral upper lobe infiltrates or in the form of obstructive bronchial aspergillosis or an ulcerative tracheobronchitis (Fig. 75.12 a,b,c,d). Diagnosis of pulmonary aspergillosis requires the documentation of invasion on a biopsy specimen. Treatment is with amphotericin B.

Primary pulmonary infection of the lung may be seen with histoplasmosis. The most common pulmonary manifestation of histoplasmosis however, is in the setting of disseminated disease presumably due to reactivation. Respiratory involvement typically presents with fever, fatigue, weight loss, cough, and dyspnea. Other manifestations include a nodular skin rash, oral ulcers, and diffuse micronodular pattern on chest radiograph (Fig. 75.13 a,b). The drug of choice is amphotericin B with itraconazole being a less toxic and effective alternative, which can also be used as a maintenance therapy.



**Fig. 75.12a:** *Aspergillus niger*—microscopic appearance.





**Fig. 75.12b:** Chest radiograph in aspergillosis.



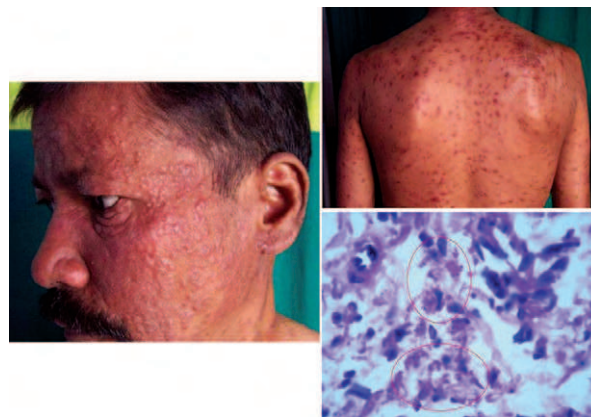
**Fig. 75.12c:** Growth of Aspergillus in culture.



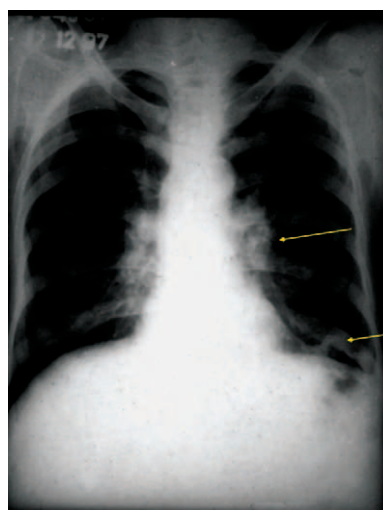
**Fig. 75.12d:** Cavity in pulmonary aspergillosis.

## PARASITIC INFECTIONS

*Toxoplasma gondii* is the most frequent parasitic pneumonia seen in persons with HIV infection who are not on ART or primary



**Fig. 75.13a:** Histoplasmosis skin eruptions.



**Fig. 75.13b:** Histoplasmosis—pulmonary involvement.

prophylaxis. The disease represents reactivation of latent infection, rather than new infection, and occurs in advanced AIDS (CD4 counts  $<100/\mu\text{L}$ ).

*Toxoplasma gondii* encephalitis is a well-recognized complication of advanced HIV disease and is an AIDS-defining condition. Although toxoplasmosis is the most common cause of focal brain abscesses in HIV-infected persons, pulmonary involvement is uncommon. Pulmonary disease may occur in persons with CNS involvement or disseminated disease or with isolated pulmonary involvement. Pulmonary toxoplasmosis characteristically presents with cough that is nonproductive, dyspnea, and fever. It may be clinically indistinguishable from PCP. Occasionally, disseminated toxoplasmosis may present with acute respiratory failure. Physical examination of the chest may be normal or may reveal crackles. Focal neurologic findings are common.

The chest radiograph usually reveals bilateral infiltrates, either fine reticulonodular infiltrates indistinguishable from PCP or a coarser nodular pattern similar to that seen with tuberculosis or fungal pneumonias. A positive toxoplasma IgG antibody and the presence of toxoplasma in BAL help in the diagnosis. Sulfadiazine plus pyrimethamine is the first-line recommended treatment

for *Toxoplasma* infection.<sup>5</sup> Leucovorin is coadministered with pyrimethamine to reduce the occurrence of hematologic toxicities from pyrimethamine. Clindamycin plus pyrimethamine (and leucovorin) and trimethoprim-sulfamethoxazole (TMP-SMX) are the main alternatives. Mortality is high (approximately 35%), in spite of treatment.

Prevention is indicated in people with CD4 cell count below 100 cells/ $\mu$ L by administration of TMP-SMX.<sup>5</sup> Dapsone plus pyrimethamine (and leucovorin) and atovaquone with or without pyrimethamine (and leucovorin) are recommended for persons who cannot tolerate TMP-SMX.

## VIRAL INFECTIONS

## Herpes Viruses

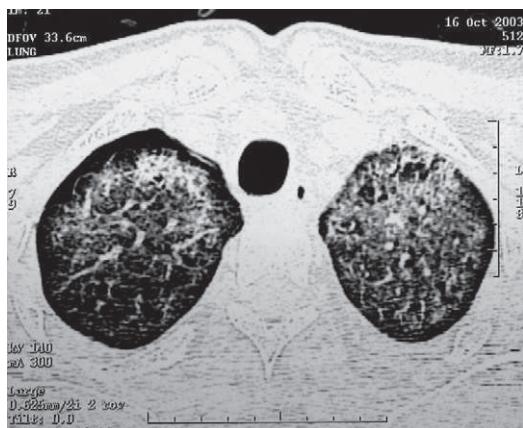
HIV infection is characterized by infections with the herpes group of viral infections. Complications usually manifest in the extrapulmonary sites.

## CMV Infections

CMV infection occurs in 100% of gay men with HIV infection and to a lesser extent in other risk groups. It usually occurs after significant immunosuppression (CD4 count less than 100 cells/ $\mu$ L). The most common manifestation of CMV disease is retinitis, although lungs, central nervous system, colon may also be involved. Pneumonitis is mainly subclinical, but clinical disease usually presents with nonspecific symptoms (Fig. 75.14).

Diagnosis is via BAL or sputum induction which reveals typical inclusion bodies in smears fixed with Giemsa or hematoxylin-eosin in 20–30% cases.

Treatment with nucleoside analogues ganciclovir, foscarnet, or cidofovir should be considered in symptomatic patients if there is documented CMV pulmonary involvement in absence of other pathogens.



**Fig. 75.14:** Cytomegalovirus pneumonia.

## Herpes Simplex Virus and Varicella Zoster Virus Pneumonitis

Herpes simplex virus (HSV) pneumonitis is very rare, and occurs as a result of either disseminated or tracheobronchial disease. Varicella zoster virus (VZV) pneumonitis is a particularly severe complication of HIV infection in children and is usually accompanied by vesicular rash. Herpes zoster is not usually accompanied by pneumonitis in adults. Diagnosis is by viral culture from appropriate respiratory secretions and histopathology. Treatment is with IV acyclovir.

## ■ Noninfectious Complications

## KAPOSI SARCOMA

Kaposi sarcoma (KS) is caused by HHV8. It is the most common malignancy associated with HIV infection. It occurs in 6–20% of HIV infected homosexual or bisexual men.<sup>26,27</sup> Lung involvement is detected in 20–40% of these patients and is usually accompanied by skin and mucosal lesions, but has been described in isolation. The malignancy may obstruct the airways directly or indirectly due to pulmonary edema as a result of lymphatic obstruction. It may cause large effusions, lung consolidation and hemorrhage.

Pulmonary involvement with Kaposi sarcoma is generally with shortness of breath, especially on exertion and cough. Stridor and hemoptysis in a patient with diagnosed mucocutaneous KS is pathognomonic of pulmonary involvement. Associated OIs are very common and complicate the clinical picture.

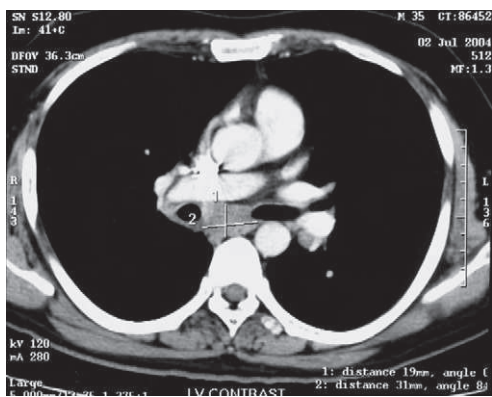
Radiographic appearances can be as the focal infiltrative lesions, pleural effusion or mediastinal adenopathy. The chest X-ray characteristically shows bilateral lower lobe infiltrates that obscure the margins of the mediastinum and diaphragm. Red or purple lesions can be seen endobronchially during FOB. Biopsy is usually avoided because lesions are highly vascular. Treatment with cytotoxic chemotherapy is relatively unsuccessful, and palliative treatment is required for bleeding or obstructive lesions. Highly active antiretroviral therapy helps in resolution of lesions. Median survival in HIV positive patients with extensive KS is between 2 and 10 months.

## Non-Hodgkin Lymphoma (NHL)

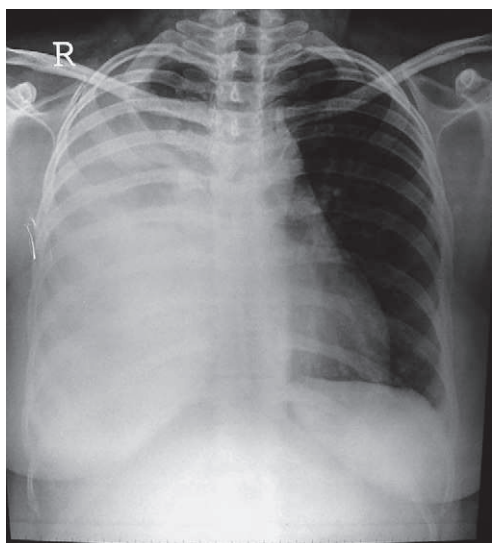
Patients with HIV-related NHL present with symptoms of night sweats, fever, and weight loss; usually when CD4 counts are less than 100 cells/ $\mu$ L. Disease is often extranodal, although patients may have an enlarging mass on a chest radiograph (Fig. 75.15 a,b).

## OTHER MALIGNANT CONDITIONS

Primary lung tumors are occasionally associated with HIV infection.<sup>28</sup> Other tumors such as Hodgkin lymphoma, multiple myeloma, and metastases from brain tumors and seminomas were unequivocally associated with HIV infection.



**Fig. 75.15a:** Enlarging mediastinal mass.



**Fig. 75.15b:** Enlarging mediastinal mass in chest radiograph.

## INTERSTITIAL PNEUMONITIS

Two forms of idiopathic interstitial pneumonitis have been identified in patients with HIV infection: lymphocytic interstitial pneumonitis (LIP) and nonspecific interstitial pneumonitis (NSIP).

### Lymphocytic Interstitial Pneumonitis (LIP)

It is histologically a well-defined complication. Lymphocytic interstitial pneumonitis frequently occurs in children younger than 13 years who have been infected with HIV perinatally, but occasionally is also seen in adults (1% cases). The pathogenesis is unclear, but it is thought to be an immunological reaction to HIV or EB virus within the lung.

Signs and symptoms are nonspecific and patients develop dyspnea. Symptoms may resolve spontaneously or progress to respiratory failure. Diagnosis is by histology and exclusion of other opportunistic infections. The characteristic X-ray finding is of bilateral reticulonodular infiltrates, predominantly in the

lower lobes but rarely in the entire lung. BAL fluid reveals no organisms, but only CD8+ lymphocytes.

Lung biopsy shows firm grey nodules characterized by lymphocytic infiltrate. Though granulomas are not seen lymphocytic infiltrate with germinal center formation may be seen. This condition is generally self limited and no specific treatment is necessary. In severe cases, antiretroviral therapy, intravenous immunoglobulin and corticosteroids have been tried.

## Nonspecific Interstitial Pneumonitis (NSIP)

This entity is well-described in adults with HIV, and is 10 times commoner than LIP. The radiographs show bilateral reticulonodular infiltrates in most patients, while histology shows an interstitial inflammatory infiltrate with a predominance of lymphocytes and plasma cells. In contrast to LIP, a follicular pattern with germinal center formation is not seen. The etiology of this condition is not known, but it may occur as a result of previous opportunistic infections or as an immune response to HIV in the lung. There are no specific clinical features; symptoms are mild and condition may resolve or stabilize spontaneously.

## Nonspecific Emphysematous Disease

The presence of radiological changes of cystic lesions (blebs, bullae, and pneumatoceles) in the lungs of patients with HIV is called as emphysema like disease or cystic lesions. The cause is unknown; the potential etiologies include IV drug abuse, recurrent infections, and direct effect of HIV infection.

Abnormalities in airway function: These are usually mild and reversible with bronchodilators. Bronchiolitis obliterans organizing pneumonia does not show a higher incidence in HIV-positive population and the presentation is same as in HIV-negative population.

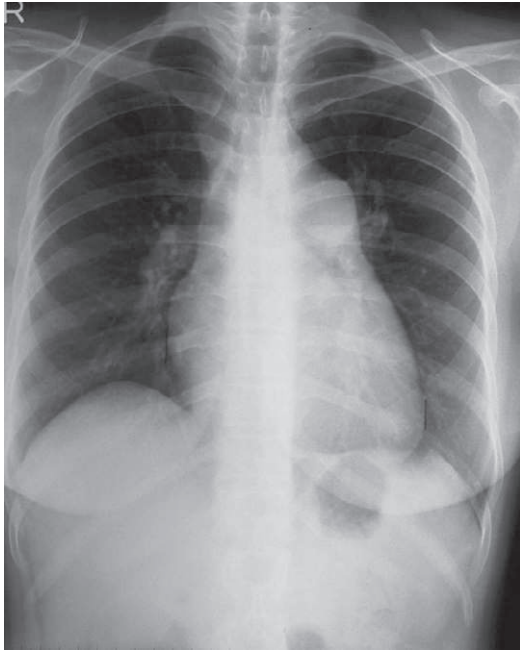
## PRIMARY PULMONARY HYPERTENSION

Incidence of this entity in HIV positive population is 1:200. There is no correlation with stage of HIV or occurrence of opportunistic infections. As compared to immunocompetent patients with primary pulmonary hypertension, patients with HIV related disease are younger, less dyspneic and have lower peak pulmonary artery pressure.

Pulmonary hypertension in HIV infection occurs due to release of epidermal growth factors which leads to induction of nitrous oxide that causes increased vessel tone and endothelial proliferation. Secondly, it can also occur due to obstructive talc granulomas in small pulmonary arteries in IV drug users and pulmonary hypertension associated with chronic liver disease and portal hypertension.

Clinical presentation is nonspecific with atypical chest pain and dyspnea on exertion. The clinical signs of pulmonary hypertension may be evident (Fig. 75.16). Echocardiography and right heart





**Fig. 75.16:** Primary pulmonary hypertension.

catheterization with pulmonary arteriogram may be necessary to confirm the diagnosis. Antiretroviral therapy does not appear to be of clear benefit, but the disease may respond to epoprostenol. However, the prognosis is quite poor with a median survival range of 2 years.

## PULMONARY MANIFESTATIONS OF IRIS

Immune reconstitution inflammatory syndrome (IRIS) may occur within days or weeks after the initiation of HAART (early IRIS) or weeks after the initiation of HAART (late IRIS).<sup>2</sup>

### Mycobacterial Infections

Tuberculosis is among the most common diseases associated with IRIS. The onset of IRIS related to *Mycobacterium tuberculosis* is usually in the first 2–3 weeks after starting HAART and typically within the first 2 months of therapy.<sup>30,31</sup> Most cases represent paradoxical cases of IRIS as the majority of cases develop in patients who are improving on therapy for known TB, but are subsequently found to be HIV-infected and therefore begun on HAART.<sup>28</sup> Pulmonary involvement may be encountered in 84% cases.<sup>32</sup> Radiographic infiltrates may worsen in areas of prior disease in 50% of the cases or may reflect new areas of involvement.

Pulmonary complications with MAC have been described in 20% cases as a part of IRIS. Specific manifestations include new infiltrates on chest X-ray, inflammatory masses, cavitary lesions, and endobronchial lesions.<sup>30,32,33</sup>

### Fungal Infections

Cryptococcus associated IRIS with pulmonary involvement is seen in 20% cases. Chest X-ray findings include diffuse infiltrates and nodules. Pleural effusions are rare. Worsening

of *Pneumocystis jiroveci* pneumonia following the initiation of HAART has been described in several case series.<sup>34,35</sup> Manifestations of IRIS in patients consist of fever, worsening hypoxia, and alveolar opacities on chest X-ray. Bronchoalveolar lavage shows lymphocytosis with elevated CD4 and CD8 T cell counts.<sup>34</sup> Potential risk factors for the development of PCP-associated IRIS are severe pneumonia on presentation ( $\text{PaO}_2 < 70$  mmHg), marked decrease in HIV viral load on initiation of highly active antiretroviral therapy (HAART), close proximity of HAART to PCP treatment and cessation of steroids prior to initiation of HAART.<sup>34</sup>

Histoplasmosis-associated IRIS has been infrequently reported with atypical presentations of disseminated disease. Findings include pulmonary nodules and mediastinal adenopathy.

Only one case of pulmonary aspergillosis with worsening of lung infiltrates and inflammation suggestive of IRIS has been reported till date.<sup>35</sup>

### Viral Infections

Pulmonary complications of IRIS due to viral infections appear to be less common than those due to mycobacterial or fungal infection.

### Sarcoidosis

Most cases of sarcoidosis have occurred in context of a significant decrease in HIV viral load and increase in CD4 count lending support to the possibility that sarcoidosis may reflect a form of IRIS in these patients.<sup>36</sup> Pulmonary manifestations include restrictive and obstructive ventilatory defects with decrease in diffusing capacity on pulmonary function testing. Chest X-ray findings include parenchymal opacities which can include small micronodules, ill-defined lesions, cavitary nodules, or cysts. Nodules are usually distributed in subpleural regions and along bronchovascular bundles.

### Malignancy

Kaposi sarcoma may present as a manifestation of IRIS, and rarely non-Hodgkin lymphoma (NHL) may develop or worsen as a manifestation of IRIS.<sup>37</sup>

### Treatment of IRIS

Treatment includes continuation of primary therapy against the offending pathogen in order to decrease the antigenic load, continuation of effective HAART, and judicious use of anti-inflammatory agents.<sup>38</sup>

1. Milder IRIS: Continue HAART, antimicrobial agents, and nonsteroidal anti-inflammatory drugs.
2. Severe life-threatening IRIS: Needs oral prednisolone, approximately 1–2 mg/kg. The exact duration and dose of the steroid is variable and depends upon clinical severity. Sometimes the duration of the steroid therapy may extend to 6 months or even 1 year. Consider discontinuation of HAART

in case of severe life-threatening IRIS (e.g., encephalitis, ARDS, cerebritis, and perilesional cerebral edema).

The occurrence of IRIS does not require any modification in the treatment of OIs. Maintenance treatment for OIs should not be changed and previously completed OI treatment (e.g., for tuberculosis) should not be reinitiated. Also, the dosages of chronic suppressive treatment for an OI should not be increased.

### Summary

- Apart from increased incidence of upper respiratory tract infections such as otitis media and sinusitis, recurrent bacterial pneumonias are also common in HIV disease. Common causes are *S. pneumoniae*, *H. influenzae*, *Pseudomonas aeruginosa*, and *S. aureus*. Atypical pathogens like *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydia* are other rare causes. Clinical, radiological presentation and treatment are similar to non-HIV individuals. Apart from bacterial pneumonias, mycobacterial infections are of great relevance in India.
- *M. tuberculosis* is the single most commonly seen co-infection in HIV-infected individuals in India. TB and HIV share a symbiotic association, and TB can occur at any stage of HIV disease. The clinical presentation in patients with lower CD4 counts includes disseminated lesions, resemblance to PCP, and associated extrapulmonary involvement. Microbiological analysis of respiratory secretions, radiography, and newer molecular techniques are essential for diagnosis. Treatment of drug-susceptible tuberculosis is generally as effective in HIV infected patient as it is in the general population, but modifications taking into consideration drug interactions should be done. MDR/XDR tuberculosis should be suspected in retreatment/defaulters/non-responders and close contacts of MDR TB. Treatment should include at least three drugs to which organism is sensitive and should be continued for at least 2 years or 12 months beyond sputum conversion, whichever is later.
- MAC are the group of organisms that are ubiquitous in the environment, and infection occurs when CD4 count is less than  $0.1 \times 10^9/L$ . Pulmonary involvement occurs as a part of multisystem disease. The infection is resistant to first-line antituberculous therapy, but like tuberculosis requires combination therapy with at least three active drugs, and therapy should continue lifelong unless appropriate ART is instituted.
- As HIV disease progresses with diminishment in CD4 counts, other pathogens present with pulmonary involvement. CD4 counts less than 200/microliter considerably increase the chances of PCP. Classical clinical presentation is with fever, night sweats, progressive dyspnea, and chest pain. Diagnosis is based on the demonstration of *Pneumocystis jirovecii* in respiratory secretions in conjunction with radiological and enzymatic analysis.
- Apart from these common conditions, fungal pneumonias caused by *Cryptococcus*, *Aspergillus* and *Histoplasma* spp. may be seen. Toxoplasmosis may also present with pulmonary involvement, while herpes virus infections may also involve the lung. The diagnosis of these rarer conditions requires a high index of suspicion and strong microbiologic support. Treatment of these conditions requires a multidisciplinary approach involving a pulmonologist.
- Non-infectious complications include malignant complications like non-Hodgkin lymphoma, Kaposi sarcoma, and idiopathic interstitial pneumonitis including lymphocytic and non-specific interstitial pneumonitis.
- Most common pulmonary manifestations of IRIS include mycobacterial infection. Cryptococcal lung disease may emerge in 20% cases. Rarely, sarcoidosis, Kaposi sarcoma, and other lymphomas may manifest. Treatment includes continuation of primary therapy against offending agents to decrease the antigenic load, as well as effective HAART and judicious use of anti-inflammatory agents.

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# Neurological Manifestations of HIV

Arun B. Shah • Ramshekhar Menon

## 76

### Introduction

The availability of potent therapy for human immunodeficiency virus (HIV) infection (highly active antiretroviral therapy [HAART]) has dramatically changed the outlook for infected patients. Opportunistic infections including those that affect the central nervous system (CNS) are very common in developing and under developed countries which harbor the major disease burden of HIV infection, especially in those patients who are not receiving antiretroviral therapy. The 2006 estimates suggest national adult HIV prevalence in India is approximately 0.36%, amounting to between 2 and 3.1 million people. While neurological disease may be the presenting manifestation in 7–20% of cases, the prevalence of neurological complications is about 40–70%.<sup>1,2</sup> Besides its association with opportunistic infections (OI), HIV itself can infect the central and peripheral nervous system, even in patients on HAART (Table 76.1). In a large study from India, neurological complications were seen in 20.4% of outpatients as opposed to 44.5% of hospitalized HIV-positive patients.<sup>3</sup> The most common manifestation was peripheral neuropathy (28.3%), followed by meningitis (17.9%) and central nervous system (CNS) mass lesions (16%), of which toxoplasmosis was the most common. In another study, OI of CNS (cryptococcosis, tuberculosis, toxoplasmosis, pyogenic meningitis, and neurosyphilis) were reported to be 4 times more common than noninfectious lesions, like HIV-associated dementia.<sup>4</sup> Survival after the diagnosis of HIV infection is strongly correlated with the initial acquired immunodeficiency syndrome (AIDS) defining diagnosis.<sup>1</sup> Specifically patients suffering from neurological OI or primary CNS lymphoma (PCNSL) have shorter survival rates.<sup>5</sup> In addition low CD4+ counts, anemia, lower functional status, female sex, and older age are also associated with shortened survival.<sup>5</sup> Table 76.2 shows a comparison of the incidence rate in the pre-HAART era with the present day scenario. In other studies involving homosexuals and drug users with HIV infection a similar drop in incidence rate for HIV dementia and opportunistic infections, e.g., toxoplasmosis has been noted, when compared with the period prior to 1996 with

the subsequent years.<sup>6</sup> However, another recent study showed that the incidence of progressive multifocal leukoencephalopathy (PML) did not significantly differ between the pre-HAART and

**Table 76.1:** Neurological Spectrum of HIV

(A) Primary HIV related	Stage of infection
1. Aseptic meningitis (seroconversion)	Early
2. Acute HIV encephalitis	Early
3. AIDP/CIDP	Early
4. Distal sensory polyneuropathy	Late
5. AIDS dementia	Late
6. Myelopathy	Late
7. Myopathy	Late
Unconfirmed Associations	
<ul style="list-style-type: none"><li>• Multiple sclerosis like disorders</li><li>• Cerebrovascular diseases: ischemic and hemorrhagic associated with structural changes in vasculature</li><li>• Pain disorders: primary HIV-induced headache, neuropathic pain secondary to myelopathic and neuropathic syndromes</li><li>• Psychiatric disorders: delirium, mood disorders, psychosis, and psychoactive substance use disorders, efavirenz – associated nightmares</li><li>• Seizures/epilepsy</li></ul>	
(B) Opportunistic infections	
Toxoplasmosis Cryptococcosis Progressive multifocal leukoencephalopathy (PML) Cytomegalovirus (CMV) Varicella zoster (VZV) Herpes simplex (1 and 2) Syphilis Tuberculosis: <i>M. tuberculosis</i> and atypical mycobacteria	
(C) Neoplasms	
Primary CNS lymphoma Kaposi sarcoma	
(D) Metabolic/toxic	
Hypoxic and metabolic encephalopathy Narcotic overdose Nucleoside neuropathy Zidovudine myopathy	

AIDP, acute inflammatory demyelinating polyradiculoneuropathy; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy.

**Table 76.2:** Mean Incidence Rate of HIV-1 Associated Neurologic Diseases during Three Time Periods in the Multicenter AIDS Cohort Study<sup>6</sup>

Disease	1990–92 (Monotherapy)	1993–95 (Dual therapy)	1996–98 (HAART)
HIV dementia	21.1	17.8	10.5
Cryptococcal meningitis	5.0	2.5	1.5
Toxoplasmosis	5.4	3.8	2.2
PML	2.0	1.8	1.5
CNS lymphoma	2.8	4.3	0.4

HAART period, although a prolonged survival of PML cases was noted.<sup>7</sup> One has to keep in mind the fact that a host of diseases can occur simultaneously in an immunocompromised host.

The first report of neurological involvement in an HIV-infected patient from the subcontinent was in August 1986—transmission associated AIDS dementia.<sup>8</sup> However in this patient, present criteria for HIV encephalopathy were not met as the fundus evaluation favored toxoplasmosis/tuberculosis. This however highlighted the beginning of AIDS epidemic as was smoldering

in the rest of the world. What is evident now is that the main burden of the disease, especially in the subcontinent, is due to OIs with relatively high mortality. In the era of HAART with better control of OIs and advances in diagnostic facilities the primary HIV-related illnesses are being detected, though less in comparison. Still the accessibility of HAART in a developing country like India remains frugal, necessitating greater state and social responsibility to ensure it reaches the needy.

## Neuropathology and Pathogenesis

The CNS is protected from infectious pathogens and circulating toxins by the blood–brain barrier (BBB), or the blood–nerve barrier in the peripheral nervous system. Lentiviruses such as HIV enter the nervous system through a process termed *neuroinvasion*.<sup>9</sup> HIV-1 infects leukocytes in the periphery by way of engagement of the CD4 molecule coupled with the chemokine coreceptor CXCR4 or CCR5. Antibodies to galactosyl ceramide inhibit entry of HIV into neural cell lines. The infected leukocytes subsequently cross the BBB, thereby transporting the virus into the nervous system much like a Trojan horse.<sup>10</sup> In the nervous system, HIV infects infiltrating macrophages, microglia, and astrocytes, indicative of *neurotropism*. It does not infect neurons, oligodendrocytes, or

**Table 76.3:** Differential Diagnosis of Clinical Syndromes

<b>HIV-associated meningitis</b>	
<ul style="list-style-type: none"> <li>Aseptic HIV meningitis</li> <li>Cryptococcal meningitis</li> <li>Tuberculous meningitis</li> <li>Syphilitic meningitis</li> <li><i>Listeria monocytogenes</i> meningitis</li> <li>Lymphomatous meningitis</li> </ul>	
<b>HIV-associated diffuse encephalopathy</b>	
<ul style="list-style-type: none"> <li>HIV-associated dementia</li> <li>HIV-associated minor cognitive motor dysfunction</li> <li>HIV demyelinating leukoencephalopathy</li> <li>Acute encephalopathy associated with IRIS</li> <li>Toxoplasmosis encephalitis</li> <li>CMV encephalitis</li> <li>Herpes encephalitis (Fig. 76.2)</li> <li>Metabolic encephalopathy</li> <li>Focal brain lesions causing intracranial hypertension</li> </ul>	
<b>HIV-associated focal brain dysfunction</b>	
<ul style="list-style-type: none"> <li>Cerebral toxoplasmosis</li> <li>Primary CNS lymphoma</li> <li>Progressive multifocal leukoencephalopathy</li> <li>Tuberculoma</li> <li>VZV encephalitis</li> <li>Stroke: Vasculitis vs thrombophilic state</li> </ul>	
<b>Spinal cord disease</b>	
<ul style="list-style-type: none"> <li>Acute presentation: <ul style="list-style-type: none"> <li>vertebral tuberculosis</li> <li>transverse myelitis (sometimes due to VZV)</li> <li>Spinal meningitis (TB)</li> <li>Intraspinal (intramedullary or extradural) lymphoma</li> </ul> </li> <li>Chronic/subacute <ul style="list-style-type: none"> <li>progressive radiculopathy CMV</li> <li>vacuolar myelopathy</li> <li>Compressive myelopathy</li> </ul> </li> </ul>	
	<ul style="list-style-type: none"> <li>Human T-cell lymphoma virus-1 (HTLV-1) associated myelopathy</li> <li>Nutritional</li> </ul>
<b>Peripheral neuropathy</b>	
Early stages (immune dysregulation)	
<ul style="list-style-type: none"> <li>AIDP</li> <li>CIDP</li> <li>Vasculitic neuropathy</li> <li>Brachial plexopathy</li> <li>Lumbosacral plexopathy</li> <li>Cranial mononeuropathy</li> <li>Mononeuritis multiplex</li> </ul>	
Mid and late stages (HIV replication driven)	
<ul style="list-style-type: none"> <li>Distal sensory polyneuropathy</li> <li>Autonomic neuropathy</li> <li>Motor neuron disease</li> </ul>	
Late stages (OI, malignancy)	
<ul style="list-style-type: none"> <li>CMV polyradiculomyelitis</li> <li>Syphilitic polyradiculomyelitis</li> <li>Tuberculous polyradiculomyelitis</li> <li>Lymphomatous polyradiculopathy</li> <li>Zoster ganglionitis/radiculitis</li> <li>CMV mononeuritis multiplex</li> <li>AIDS cachexia neuropathy</li> <li>Amyotrophic lateral sclerosis (ALS) like motor neuronopathy</li> <li>Nutritional neuropathy (vit B<sub>6</sub>, B<sub>12</sub>)</li> </ul>	
All stages (toxic neuropathy)	
<ul style="list-style-type: none"> <li>Nucleoside RT inhibitor (ddI, ddC, d4T)</li> <li>Other drugs: vincristine, INH, ethambutol, thalidomide</li> </ul>	
<b>Myopathy</b>	
<ul style="list-style-type: none"> <li>Polymyositis</li> <li>Inclusion body myositis</li> <li>Toxic (Zidovudine) myopathy</li> <li>AIDS-cachexia myopathy</li> </ul>	

Schwann cells. This process culminates in cell injury and death involving neurons, astrocytes, and neural stem cells.<sup>11,12</sup>

The pathologic hallmarks of advanced HIV infection of the CNS include HIV encephalitis, defined by multinucleated giant cells, viral antigen detection, perivascular cuffs, and diffuse white matter pallor.<sup>13</sup> Neurovirulence results in neuronal cell death and also synaptodendritic “pruning”.<sup>14</sup> Activation of monocyte lineage cells result in production of procytokines, eicosanoids, nitric oxide, and quinolinic acid which are neurotoxic. Although it is true that the consistent host response to HIV infection is neuroinflammation, each host mounts a distinct profile of immune gene activation in the nervous system based on the host’s unique genotype and phenotype. Specific brain derived HIV-1 sequence is associated with enhanced *in vivo* and *ex vivo* neurovirulence. Molecular sequence diversity is significantly greater in viruses derived from blood and brain in demented patients compared with nondemented AIDS patients, suggesting that the diversity contributes significantly to the neuro-toxicity.<sup>15,16</sup> Diversity is caused by the error prone reverse transcriptase, high rates of replication, in permissive cells, intense immune selection, and recombination between closely related and disparate viral strains.<sup>17</sup> Of interest, HIV can segregate into organ-specific strains within a single host that act in concert to escalate the disease course; e.g., immunosuppressive and neurovirulent viral strains cooperating within a single host.<sup>18</sup> Table 76.3 emphasizes the neuropathological heterogeneity of HIV infection leading to multiple sites of affliction by the virus directly or due to opportunistic infections arising out of the immunocompromised state.

Overall, considering the myriad of diagnostic possibilities in an HIV-infected patient, Figure 76.1 should be useful to the clinician to approach, investigate, and arrive at a diagnosis. Site specific diseases will be discussed further.

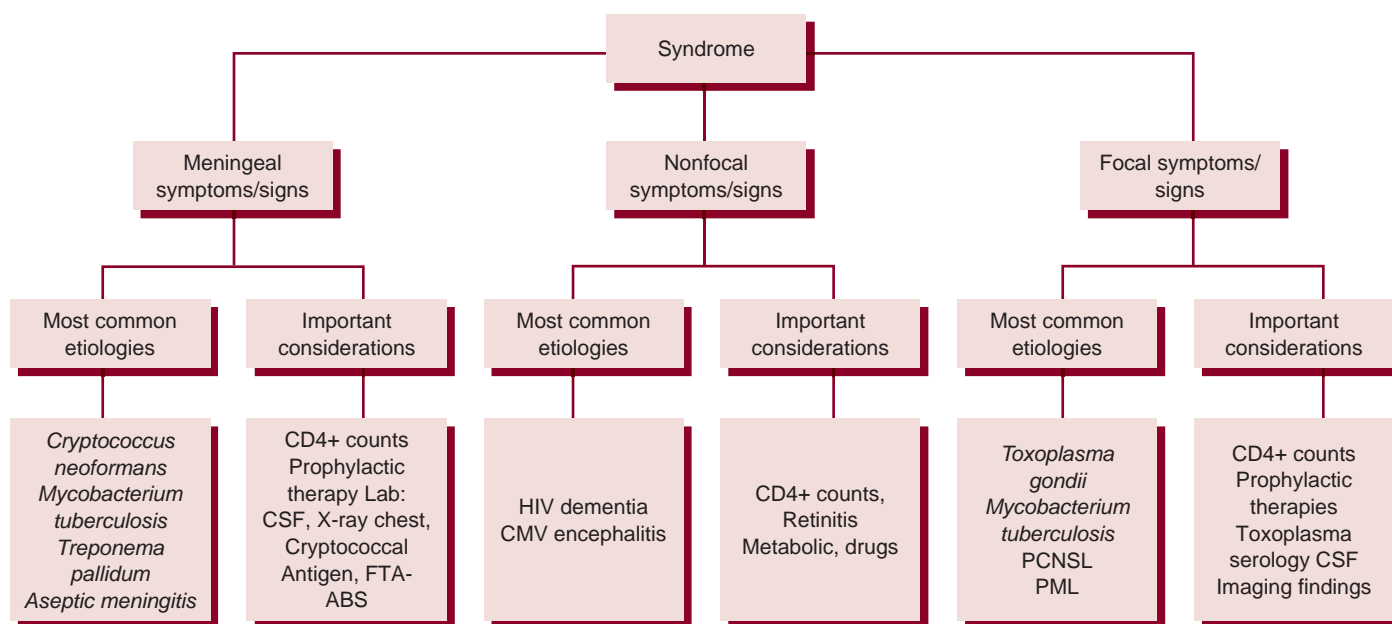
## Site Specific Diseases

### MENINGITIS

#### Aseptic Meningitis

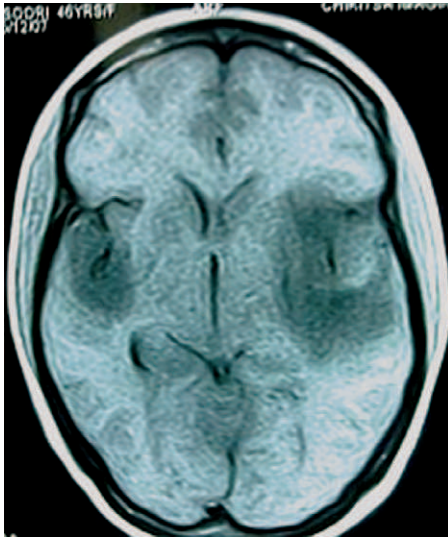
It is usually a consequence of primary HIV infection as part of seroconversion illness. The onset varies from 2 to 4 weeks after exposure but can appear as early as 6 days or as late as 6 weeks. Common associated symptoms during the seroconversion phase include fever, generalized adenopathy, myalgias, arthralgias, truncal rash, and headache. It has also been shown that subclinical meningitis may be seen in a subset of patients who underwent lumbar puncture for other reasons.<sup>19</sup> Laboratory data also indicate that mild mononuclear pleocytosis may be seen in up to 18% of asymptomatic patients.<sup>20</sup> CSF analysis reveals elevated protein (less than 100 mg/dL) usually mild, mononuclear pleocytosis (>25/ $\mu$ L). Exclusionary studies (cryptococcal antigen, bacterial/viral cultures, polymerase chain reaction, and cytology) are necessary and the significance of CSF HIV-1 RNA estimation is unknown. In acute meningitis, symptoms of fever, headache, and meningeal signs resolve within 1 month. Patients of chronic meningitis are usually afebrile, suffer from headaches while some patients may suffer seizures, confusion, cognitive deficits cranial nerve palsies, and idiopathic intracranial hypertension<sup>21</sup> and its relation to HIV is usually a diagnosis of exclusion.

Similarly, encephalitis as a complication of seroconversion illness usually is a post febrile encephalopathy with seizures and some cases coma. It resolves in 2–3 weeks. Fatal necrotizing leukoencephalopathy and meningoencephalitis due to either cessation of HAART or loss of the host’s ability to control



**Fig. 76.1:** Approach to CNS infection in HIV + patient. Adapted from Ref no. 22.





**Fig. 76.2:** HSV-2 encephalitis: T1 weighted MRI of a seropositive patient presenting with seizures followed by global encephalopathy. CSF was consistent with a hemorrhagic meningitis. Hypointensities are seen over bilateral temporal cortices and limbic regions. CSF HSV-2 DNA PCR was positive. CD4+ counts of 380/mm<sup>3</sup>.

chronic CNS HIV have also been described.<sup>22</sup> Improvement after change of HAART regimen has been noted. Other encephalitic illnesses need to be ruled out in this setting as evident from Figure 76.2.

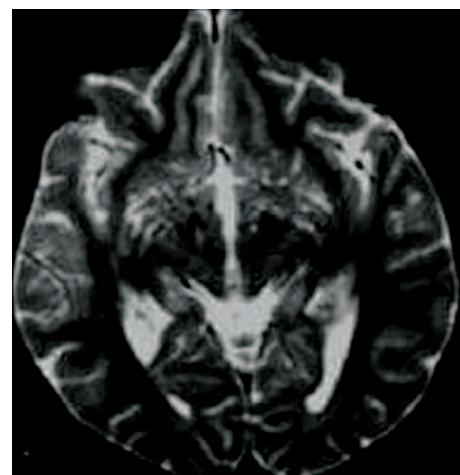
### Cryptococcal Meningitis

It is the most common manifestation of systemic fungal infection in HIV-infected persons, especially in the developing world; in some areas, it is the second most common OI after tuberculosis. The CD4+ cell counts are usually <100 cells/mm<sup>3</sup>. It is caused by the encapsulated yeast like fungus *Cryptococcus neoformans* var. *neoformans*, acquired from the soil and feces of birds via inhalation and subsequent dissemination from lungs to other organs. Cerebrospinal fluid (CSF) is particularly prone to infection because it is a good growth medium and lacks complement and immunoglobulin. Theories behind its pathogenesis include dissemination of newly acquired infection, reactivation of latent infection due to immunosuppression, and reactivation of latent infection due to immune reconstitution syndrome. Enhanced immune function secondary to HAART may unmask latent infection and precipitate clinically apparent meningitis.

A large series of 335 HIV-seropositive patients with cryptococcal meningitis revealed headache with intracranial hypertension to be the predominant clinical feature.<sup>23</sup> Others include fever, altered sensorium and seizures. Papilledema was the dominant clinical sign. One third of the patients had disseminated infection in the lungs, kidney, or skin. Cranial neuropathies and focal deficits were seen in a small subset of patients. Neuroimaging is to be carried out in all suspected cases of chronic meningitis. While majority of the scans may be normal, they may show diffuse

cortical atrophy, hydrocephalus, or focal masses in the form of punctuate nonenhancing foci of CSF density correlating with the presence of cryptococci in the Virchow-Robin spaces (Fig. 76.3). A lumbar puncture with manometry is the diagnostic procedure of choice. CSF analysis usually reveals lymphocytic pleocytosis with raised protein and low sugar level. India ink stain reveals encapsulated organisms. A positive fungal culture is considered to be the gold standard. This also helps to determine the fungal species and drug susceptibility in cases of recurrent infection. Antigen detection tests including latex agglutination and enzyme immunoassay are >90% sensitive and specific.

Therapeutic practice is to initiate induction therapy with amphotericin B 0.7–1 mg/kg/day plus 5-flucytosine 100 mg/kg/day for 2 weeks followed by fluconazole 400 mg/day for a minimum of 10 weeks. After this period fluconazole dose may be reduced to 200 mg/day depending on the therapeutic status of the patient. Flucytosine may not be routinely used due to lack of availability and high cost. Hence, monotherapy with amphotericin B is initiated and fluconazole added simultaneously or after 2 weeks. Monitoring of serum creatinine and potassium levels should be done frequently. Although liposomal preparations of amphotericin have many advantages such as the administration of higher doses over a short period of time with less adverse events, the cost is prohibitive. Fluconazole should be continued till the CD4+ counts exceed 350/mm<sup>3</sup> and cultures are negative. Itraconazole albeit may be less effective but may be suitable for those patients who do not tolerate fluconazole. If there is no clinical resolution after acute treatment (8–10 weeks), a repeat lumbar puncture should be done. If *Cryptococcus* is still grown from CSF, then acute treatment should be continued considering possible dose changes to the existing therapy or addition of other antifungal agents. Repeat susceptibility testing to antifungal



**Fig. 76.3:** Cryptococcomas: T2 weighted MRI showing prominent hyperintensities in the deep subcortical regions which are actually gelatinous appearing pseudocysts that extend along the enlarged perivascular spaces.

agents may be helpful in selecting the most effective drugs. Elevated intracranial pressure occurs in up to 75% of the patients with cryptococcal meningitis and is an important contributor to mortality and morbidity. Patients with raised intracranial tension should be treated aggressively. The principal intervention for reducing elevated intracranial pressure is percutaneous lumbar drainage. In patients with normal baseline opening pressure ( $<200$  mm H<sub>2</sub>O), a repeat lumbar puncture should be performed 2 weeks after the initiation of therapy to exclude elevated pressure and to evaluate culture status. In patients with elevated baseline opening pressure, lumbar drainage should be done to reduce pressure by 50%. Daily lumbar punctures are carried out to maintain CSF opening pressure in the normal range. Once CSF pressure is normal for several days, lumbar puncture can be stopped. When frequent lumbar punctures are required or fail to control symptoms of elevated intracranial pressure, a lumbar drain may be considered. Ventriculoperitoneal shunting may be considered when the above measures fail to control raised intracranial pressure and also in patients with hydrocephalus.<sup>23</sup>

Antiretroviral therapy is usually started when the clinical condition of the patient is relatively stable especially in those with very low CD4+ ( $<100$  cells/mm<sup>3</sup>) counts. The possibility of immune reactivation inflammatory syndrome (IRIS) should be considered when patients develop new neurological deficits with an improving CD4+ count.<sup>24</sup> Patients with cryptococcal IRIS can present as meningitis, intracranial mass lesions, pulmonary cavitation, or lymphadenitis.<sup>25</sup> It usually occurs after a few weeks or a few months and is treated with steroids or nonsteroidal anti-inflammatory drugs (NSAIDs).

The poor prognostic factors are depressed levels of consciousness, signs of raised intracranial pressure, depressed CSF cell counts and glucose levels and CSF cryptococcal antigen titer  $> 1024$ .<sup>26</sup> A significant proportion of patients can develop various neurological sequelae, which include visual loss, decreased mental capacity, hearing loss, permanent cranial nerve palsies, and hydrocephalus.<sup>23</sup>

## Syphilitic Meningitis

In patients with HIV infection, neurosyphilis appears to develop within a shorter interval than is usual for development of the disease. In addition, the prevalence of acute syphilitic meningitis, ocular symptoms or signs (particularly uveitis), and hearing loss is increased. Asymptomatic patients with positive serologic findings should undergo CSF examination for exclusion of neurosyphilis. The recommended treatment for neurosyphilis consists of a 10- to 14-day course of either aqueous crystalline penicillin G, 3 to 4 million units IV every 4 hours or procaine penicillin, 2.4 million units IM daily, with oral probenecid, 500 mg 4 times a day. In patients who are allergic to penicillin, desensitization should be considered. Alternatively, ceftriaxone, 2 g IV or IM daily, or amoxicillin, 3 g plus probenecid, 500 g twice a day can be given for 15 days. CSF examination should be repeated at 3–6 monthly intervals for the first year and then every 6 months,

up to 2 years. Ideally, the CSF cell count should normalize and the protein levels also become lower, but the coexistent HIV infection may preclude this. However, a declining VDRL titer in CSF confirms adequacy of treatment.

## Tuberculous Meningitis

HIV infection increases the risk of tuberculosis, and it was anticipated in the year 2000 that 14% of the 10.2 million newly detected cases of tuberculosis would be in patients with HIV infection.<sup>27</sup> Extrapulmonary disease is more common in patients with advanced immune compromised. TBM is the most serious manifestation of tuberculosis and is one of the three most common neurological OIs seen in India.

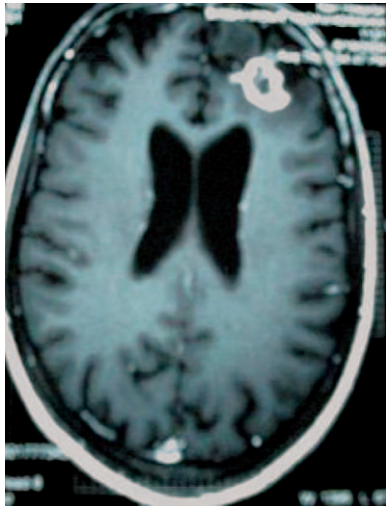
A large pathology series in Western India revealed a reduced inflammatory response in the meninges, with a paucity of basal exudates which is in tandem with the minimal meningeal enhancement seen on CT scans.<sup>28</sup> Microscopic infarcts secondary to arteritis were seen in the basal ganglia and parenchyma. AFB was present in large quantities within the lesions. This paucity of immune response was also reflected in the CSF.

Presenting symptoms include fever, headache, vomiting, weight loss, seizures, and impaired vision. Meningeal irritation, hemiplegia, and paraplegia are infrequent compared to seronegative patients. Cranial neuropathies are significantly more common, especially in advanced stages of infection. It is thus a more rapid and fulminant disorder. Clinical difference is probably evident between Indian patients and those from the West as the former are significantly more immunocompromised.<sup>28</sup>

CSF may not be as reactive as in immunocompetent patients, thus rendering the diagnosis of TBM presumptive. However, serial large volume cultures may increase the yield of detection, and identification by polymerase chain reaction (PCR) is specific but not sensitive (Table 76.4). CSF adenosine deaminase (ADA) activity measurement of more than 5 IU/L has a sensitivity of 60–80% and specificity of 70–90%. Tests like CSF tuberculostearic acid, blood gamma-interferon levels, and BACTEC culture are reported to improve detection corroboratively. Neuroimaging may show communicating or noncommunicating hydrocephalus. It may also demonstrate infarcts, tuberculomas (Fig. 76.4), and tuberculous abscesses. Identification of active tuberculosis at

**Table 76.4:** CSF Diagnostic Tests Available for TBM<sup>7</sup>

	Sensitivity
Acid-fast staining of bacteria	5–25%
Tuberculostearic acid	50–75%
Mycobacterium isolation from routine single lumbar puncture	20–40%
Mycobacterium isolation from 3 high-volume lumbar punctures	50–80%
Polymerase chain reaction assay detection of nucleic acid	50–75%
Detection of antibody to <i>M. tuberculosis</i>	55%



**Fig. 76.4:** Intracranial tuberculoma: An intensely ring-enhancing lesion over the left frontal region which was hypointense on T1 and T2 images. This seropositive patient had systemic evidence of tuberculosis.

another anatomical site aids the diagnosis though parallel tracking (infection by multiple pathogens) is notorious in HIV-infected hosts.

Three or more drugs are required for a minimum period of 12 months in established cases. Duration of therapy may need to be prolonged (up to 18–24 months) especially in those with coexistent tuberculomas. First line drugs include isoniazid (5–10 mg/kg/day; not >300 mg/day) and rifampicin (10 mg/kg/day; not >600 mg/day); Rifabutin is preferred if protease inhibitors are part of the HAART regimen. Two additional drugs need to be given during the first 3 months. Pyrazinamide (15–30 mg/kg/day) is given along with either streptomycin (15 mg/kg/day) or ethambutol (15–25 mg/kg/day). Atypical mycobacteria may require usage of second line drugs, e.g., ciprofloxacin (1500 mg/day), ethionamide (500–1000 mg/day), rifabutin, kanamycin, or cycloserine. Multidrug resistance, defined as resistance to at least isoniazid and rifampicin, is most common in patients infected with HIV, and the death rate is much higher when these organisms cause meningitis.<sup>29</sup> Steroids are added in cases presenting with altered mentation, focal signs, and coexistent tuberculomas especially those >2 cm in size. A recent study showed that while steroids significantly reduced the risk of death, they did not reduce the disability 9 months after treatment initiation.<sup>30</sup> Of note, survival benefit was not observed in the HIV-infected patients enrolled in the study. Deaths among the HIV-infected subjects occurred at a constant rate throughout follow-up. This observation, combined with the fact that none of the HIV-infected subjects in the study received HAART, suggests that HIV infection was a major contributor to death.

Even before the advent of HAART, “paradoxical responses” were noted in patients undergoing treatment for TBM. Such individuals developed CSF polymorphonuclear pleocytosis or brain tuberculomas early in course of treatment, presumably due

to improved ability to respond immunologically or to greater antigenic stimulation as a result of bacterial death. IRIS in patients undergoing treatment for pulmonary or lymphatic tuberculosis is well-documented. Active infection must always be excluded. Preferably, treatment for tuberculosis should take priority over that for HIV infection in HIV-infected tuberculosis, and HAART may be administered after the treatment of tuberculosis, but simultaneous layering with other infections may render the decision difficult.

Though it is believed that HIV-infected patients with TBM have a higher mortality rate, there are no studies that have examined the course of the disease in HIV-infected patients treated with HAART.

## Other Causes of Meningitis

Meningitis secondary to *Listeria monocytogenes*, *Salmonella* sp., and organisms causing pyogenic meningitis are being seen with increasing frequency in seropositive patients. Acute meningitis therapy should thus include ampicillin in addition to the standard medications. Other causes include nocardiosis, histoplasmosis, coccidioidomycosis, mucormycosis, and disseminated candidiasis. Lymphomatous meningitis is a complication of AIDS related systemic lymphoma. The incidence of systemic non-Hodgkin lymphoma is over 100 times increased and Hodgkin disease is approximately 10 times increased in the HIV-infected population.<sup>31</sup> Factors predicting a CNS involvement include Epstein–Barr virus (EBV) infection, extra nodal disease at diagnosis, and a non-CNS relapse.<sup>32</sup> An examination of the CSF for malignant cells is mandatory in all AIDS patients with systemic lymphoma. Steroids can be effective for symptomatic treatment of headache and pain. The appropriate treatment should include intraventricular administration with an Ommaya reservoir of either methotrexate 12 mg or cytosine arabinoside 50 mg or thiotepea 10 mg biweekly until the CSF is devoid of malignant cells.

## DIFFUSE ENCEPHALOPATHIES

### HIV-Associated Dementia (HAD)

Prior to availability of therapy, up to 60% of patients with AIDS developed obvious or subclinical cognitive decline. In the era of HAART incidence of HIV dementia is reported to be only 1%<sup>33</sup> though two case series have placed the figure between 4–13%.<sup>34,35</sup> Differences in neurovirulence of HIV subtypes are believed to be responsible for variations in incidence rates between developed and developing nations.

The development of HAD is among the most devastating consequences of HIV-1 infection because of its unique and progressive clinical manifestations. Clinical and pathological severity does not correlate particularly well. Neurotoxins include the viral envelope glycoprotein gp120 and cytokines induced by systemic and cerebral HIV infection. N-methyl-D-aspartate (NMDA) receptor activation and calcium influx resulting from toxins elaborated by interactions of HIV-infected monocytes and macrophages and cytokines have been proposed as the mechanisms



**Box 76.1****Features of HIV-1 Associated Neurocognitive Disorders (HAD, Mild Neurocognitive Disorder)**

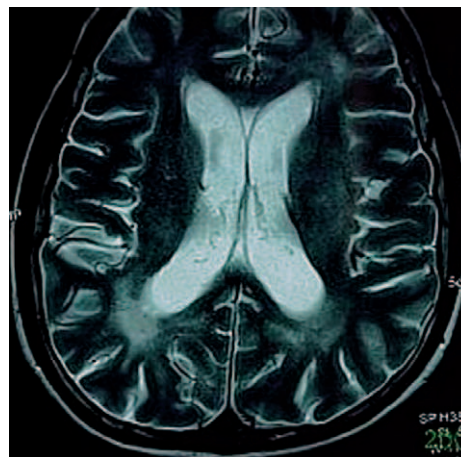
- Neurocognitive dysfunction: memory impairment, poor concentration, psychomotor slowing.
- Emotional disturbance: apathy and social withdrawal, irritability, mental inflexibility, and loss of libido.
- Motor abnormalities: weakness, ataxia, clumsy gait, tremor, bradykinesia, increase in tone, hyper-reflexia, spasticity, abnormal eye movements.

of neuronal injury. Histologically, the major changes are seen in the subcortical areas of the brain, and this possibly explains the clinical picture of “subcortical dementia”. Remarkable diversity is exhibited in its clinical presentations as shown in the table below, including movement disorders, mania, and psychosis (Box 76.1).

The diagnosis of this condition may be more difficult to make because of comorbidities such as prior substance abuse, head injury, or coinfections such as hepatitis C infection. The full spectrum of asymptomatic neurocognitive impairment remains undefined in terms of impact and outcomes; however, the diagnosis of HAD heralds a prognosis for diminished survival, regardless of whether the patient is receiving HAART.<sup>32,36,37</sup>

Symptoms typically begin once an individual's CD4<sup>+</sup> count drops <200 cells/mm<sup>3</sup>. Clinical risk factors also include high CSF or plasma viral load, anemia, extremes of age, intravenous drug abuse, and several host genetic polymorphisms.<sup>33</sup> Radiologic features accompanying HAD include cerebral and basal ganglia atrophy and diffuse periventricular white matter hyperintensities on MRI T2-weighted images (Fig. 76.5). MR spectroscopy shows diminished N-acetyl aspartate, a neuronal metabolite, together with increased choline levels indicative of inflammation. CSF analyses to rule out OIs is mandatory; high protein and immunoglobulin G levels with pleocytosis are found in CSF of 66% of HAD patients.<sup>38</sup> Viral load in CSF appears to be predictive of HAD and is higher in demented than in nondemented HIV patients and in patients of HIV encephalitis.<sup>38</sup>

Tools for assessment and follow-up of the patients involve neuropsychological evaluation. Since HAD is a primarily subcortical dementia, it is not readily detected by the Folstein Mini-Mental Status Examination unless the patient is severely demented. Better tools include the International HIV Dementia Scale, the Mental Alteration Test, the Executive Interview, and the HIV Dementia Assessment.<sup>39–42</sup>



**Fig. 76.5:** HIV-associated dementia: Symmetrical periventricular white matter hyperintensities on T2 weighted MRI in a seropositive patient clinically diagnosed as HIV encephalopathy.

Metabolic encephalopathies including hypothyroidism and vitamin B<sub>12</sub> deficiency, medication side effects, substance abuse, and depression need to be considered while evaluating these patients. Pointers to the differential diagnosis with other opportunistic infection related encephalopathies are as in Table 76.5.

HAART regimens used in therapy consist of two nucleoside analog reverse transcriptase inhibitors (NRTIs) plus a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). Specific antiretroviral drugs have higher CSF penetration than others, including the NRTIs zidovudine (AZT), stavudine (d4T) and abacavir, the NNRTIs nevirapine, efavirenz, and the PI indinavir.<sup>43,44</sup> Combining ritonavir, a P-glycoprotein inhibitor, with indinavir may increase the latter level in the brain. In HAD, a combination of AZT/d4T (with or without lamivudine or abacavir) plus nevirapine would be an effective combination.<sup>44,45</sup> Dosage strategies are as below:

- Zidovudine 300 mg tid + any of the following:
  - Nevirapine 200 mg bid
  - Indinavir 800 mg tid
  - Efavirenz 600 mg qd
  - Nelfinavir 750 mg tid or 1250 mg bid

**Table 76.5:** HIV-Associated Dementia—Differential Diagnosis<sup>58</sup>

	HAD	CMV encephalitis	PML
<b>Features</b>	Memory disturbance, mental slowing, Gait abnormalities	Delirium, seizures, brainstem signs	Focal neurological signs
<b>Course</b>	Several months	Days to weeks	Weeks to months
<b>MRI</b>	Diffuse atrophy, symmetrical deep white matter diffuse hyperintensities	Normal or periventriculitis	Scattered asymmetrical subcortical white matter lesions
<b>CSF</b>	Nondiagnostic, immune activation less marked	PCR positive for CMV in 90%	PCR positive for JC virus in 60%

HAD, HIV-associated dementia; CMV, cytomegalovirus; PML, progressive multifocal leukoencephalopathy; PCR, polymerase chain reaction; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid.

- Alternative NRTI agents:
  - Stavudine 40 mg bid
  - Abacavir 600 mg bid
- Zidovudine-naïve: start with 300 mg tid

Indinavir dose must be increased to 1000 mg when used in combination with nevirapine, which is cytochrome P450 inducer and decreases indinavir levels by 30%.

HAART shows some benefit in reversing HAD, although poor drug penetration, drug-resistant strains and emergence of a “burnt-out” phase of the disease appear to limit its efficacy. Neuropsychological performance is however improved in AIDS patients treated with HAART.<sup>40,41</sup> Memantine and human growth hormone are some of the many agents studied in clinical trials.<sup>38</sup>

Despite the reduction in the risk of prenatal HIV transmission due to early introduction of ART in pregnancy among children who are congenitally infected with HIV, a progressive encephalopathy can develop. The prevalence of neurologic involvement in HIV-infected children can be as high as 50% depending on the level of immunosuppression and treatment, usually in the first 2 years of life. Neurologic features of congenital HIV infection include microcephaly, delayed developmental milestones, spastic paraparesis, and rarely seizures.

HAART increases survival in patients with HAD. However, a recent longitudinal study showed that HIV-infected patients treated with HAART who were cognitively impaired were significantly more likely to die than those who were not cognitively impaired and that decreased survival among those with cognitive impairment was associated with lack of suppression of plasma viremia.<sup>46</sup>

## CMV Encephalitis and Ventriculoencephalitis

Most adults have serological evidence of latent CMV infection. The incidence of CMV disease has decreased substantially in the HAART era, and is now an uncommon cause of global encephalopathy in advanced AIDS (CD4+ count <50/mm<sup>3</sup>). Prior or active disseminated disease, such as retinitis, esophagitis, or colitis, may provide important clues to the neurological diagnosis. It typically presents as a subacute evolving confusional state and can resemble HAD. Focal cerebral signs, hyponatremia, and MRI showing periventricular enhancement are factors that favor a diagnosis of CMV encephalitis. CSF abnormalities are nonspecific. Pathological findings include microglial nodules and cytomegalic cells in cortical and subcortical gray matter, thought to be consistent with hematogenous spread of CMV to brain. CMV ventriculoencephalitis manifests with brainstem signs and often occurs on the background of retinitis or polyradiculomyelopathy. Dilated ventricles are seen on MRI. CSF in such cases may reveal elevated protein, polymorphonuclear or lymphocytic pleocytosis, and normal or low glucose levels. Ependymal necrosis and subependymal gliosis are seen on histopathology. As CMV viremia is quite common in late stage AIDS, and hence detection in this setting by culture, antigen testing, or PCR from blood does not help establish the diagnosis.

Systemic CMV infection may be treated using ganciclovir,

foscarnet, and cidofovir. All these drugs have major limitations in AIDS patients in view of the side effects and their virostatic properties. Induction therapy may be initiated with ganciclovir 5 mg/kg/day IV q8h for 2 weeks followed by maintenance with 5 mg/kg/day IV for 5 days/wk. Bone marrow toxicity is to be monitored. Foscarnet may be initiated at 60 mg/kg IV q8h for 2 weeks and maintained at 90 mg/kg/day. Renal toxicity limits its dosage. Cidofovir may be commenced at 5 mg/kg/week IV for 2 weeks followed by 2 weekly maintenance doses. Neutropenia, renal failure, and ocular complications need to be monitored. Effective HAART and thereby successful restoration of the immune response against CMV is the most efficacious therapy to improve the dismal outcome in these patients.

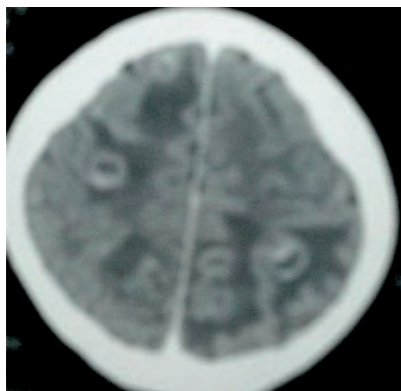
## FOCAL BRAIN DYSFUNCTION

### Cerebral Toxoplasmosis

*Toxoplasma gondii* is an intracellular parasite that can exist as tachyzoites, which are replicating organisms that cause an active disease; bradyzoites, which are nonreplicating and responsible for latent disease; and oocysts. Humans become infected by ingesting oocysts shed from cat feces or by ingesting bradyzoites in undercooked meat. Primary infection is asymptomatic in 90% of people. In the remainder, it causes a mononucleosis like illness or regional lymphadenopathy. After acute infection, organisms encyst in many tissues and persist for life. In most individuals, the only evidence of previous infection is a reactive serologic infection. In a study of 279 sera (165 healthy blood donors and 89 consecutive HIV-infected patients) from India, seroprevalence was 30.9% in immunocompetent adults and 67.8% in HIV infected. Recrudescence of toxoplasmosis occurs when CD4+ counts drop below 100 cells/mm<sup>3</sup>. In 80% of patients from the series in whom it was checked, it was above 200 cells/mm<sup>3</sup>.<sup>47</sup> Indian studies have noted that 9–28.6% of HIV patients with neurological manifestations had features consistent with toxoplasmosis.<sup>3,48</sup> Even before HAART, prophylaxis for *Pneumocystis pneumonia* with co-trimoxazole, which also provides prophylaxis against toxoplasma encephalitis, decreased its incidence. A recent study revealed that the risk of toxoplasmosis was higher in individuals who were antiretroviral naïve, who had lower CD4+ counts, and who had not received toxoplasma prophylaxis.<sup>49,50</sup>

Patients present with headache, fever, and confusion. Physical examination commonly shows fever, hemiparesis, ataxia, altered sensorium, seizures, and psychomotor retardation. Rarely, these patients have an encephalitic picture with fever and change in mental status.

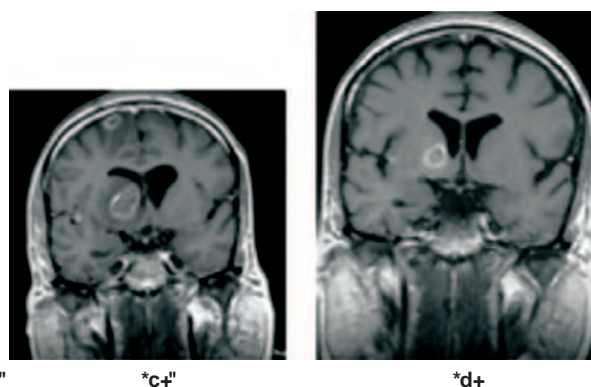
As noted earlier, a significant proportion of patients have serum IgG antibody to *T. gondii*. In general, testing for IgM antitoxoplasma immunoglobulin has little value, although it may be more likely to be positive in individuals with the encephalitic form of the disease.<sup>22</sup> Neuroimaging typically shows round lesions that are isodense or hyperdense on CT or T1-weighted MRI. These may be located at the hemispheric gray-white matter, in the deep white matter, or in the basal ganglia. More than 90% of



**Fig. 76.6:** Contrast enhanced CT brain showing multiple disc-nodular enhancing lesions over the subcortical white matter with significant perilesional edema. Serum IgG Toxoplasma antibody levels were significantly elevated.

lesions enhance with contrast in a ring, nodular, or homogenous pattern (Fig. 76.6). MRI is more sensitive than CT in identifying multiple lesions. A single lesion on neuroimaging increases the likelihood of primary CNS lymphoma, while multiple lesions increase the likelihood of toxoplasma encephalitis. Functional studies have revealed increased thallium-201 uptake are seen with lymphoma, while no brain uptake is seen in patients with toxoplasma encephalitis.<sup>22</sup> PCR detection in CSF is specific but not sensitive. Greater specificity exists in estimation of antitoxoplasm IgG in CSF by immunofluorescence.<sup>47</sup>

As toxoplasmosis is probably the most common cause of a focal brain lesion with enhancement and edema, a treatment trial is often undertaken to confirm the diagnosis. Preferable candidates for a treatment trial include those with more than one enhancing CNS lesion on neuroimaging, detectable serum antitoxoplasma IgG, not on co-trimoxazole prophylaxis and in lieu of no other more likely diagnosis. A diagnosis is established if clinical improvement is seen within 1–2 weeks and radiographic improvement is seen within 2–3 weeks after initiation of the treatment (Fig. 76.7 a,b). Unless unavoidable,



**Fig. 76.7a,b:** Cerebral toxoplasmosis (before and after treatment): A post contrast image showing two disk enhancing lesions over the right basal ganglia and parasagittal regions which regressed in size after treatment.

steroids should not be part of a treatment trial because of nonspecific radiographic improvement which may be falsely attributed to empirical therapy.

Alternative diagnosis needs to be considered in absence of improvement. If a diagnosis cannot be reached brain biopsy should be considered.

Primary therapy is commenced with pyrimethamine 100–200 mg oral loading, then 75–100 mg daily along with sulfadiazine 1.5–2 g every 6 hourly. In case of sulfa allergy clindamycin 600–900 mg orally/IV is the appropriate therapy. Folinic acid 10–50 mg orally daily should be administered in both situations. A minimum duration of 6 weeks of primary therapy may be extended until there is no evidence of active disease on neuroimaging because persistent contrast enhancement is associated with a high recurrence rate. Chronic suppressive therapy or secondary prophylaxis may be continued with pyrimethamine 25–50 mg orally daily along with sulfadiazine 1 g tid to qid. Patients on clindamycin may be continued on 300–450 mg orally tid to qid. Effective antiretroviral therapy is an important part of maintenance therapy. A recent study revealed that patients of toxoplasmosis who began HAART within 2 months of diagnosis were less likely to have progression of their HIV disease compared with patients who began HAART more than 2 months after diagnosis.<sup>49</sup> Secondary prophylaxis can be discontinued in patients with a sustained increase in peripheral blood CD4+ counts to  $>200/\text{mm}^3$  for at least 6 months.

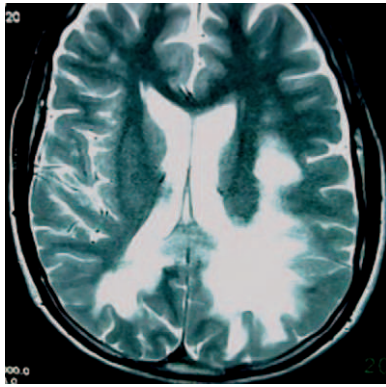
### Progressive Multifocal Leukoencephalopathy (PML)

PML is caused by the ubiquitous polyoma virus called JC virus. After infection, JC virus remains latent in blood, kidney, and perhaps in brain. The virus reactivates in the setting of immunosuppression, infects oligodendrocytes, and thus causes demyelination. It can also affect the gray matter. At least one third of the cases show perivascular round cell infiltrates as an indication of immunologic reaction. This type of reaction is considered hallmark of “slow virus” infection- typically characterized by the lack of a virus specific immune response.<sup>51</sup> The introduction of HAART led to a change in the pathology of PML, leading to a severe immune response in patients with AIDS and PML.<sup>52</sup> PML is thought to infect up to 4% of the patients with AIDS. A recent hospital based clinicoradiological study on HIV-positive patients with neurological manifestations detected that up to 14% of patients had features consistent with possible PML.<sup>53</sup>

Two case series revealed that in about 25–43% of cases, PML is the initial AIDS-defining illness.<sup>53,54</sup> Presenting symptoms and signs include limb weakness, limb incoordination, disorders of speech, and language or visual deficits. In a significant number cognitive deficits and/or a global encephalopathy may be evident. Seizures may be seen in up to 10% of patients.<sup>53</sup>

The best noninvasive method of diagnosing PML in an immunosuppressed patient is MRI. Predominantly, areas affected include the periventricular, frontal, and parieto-occipital white

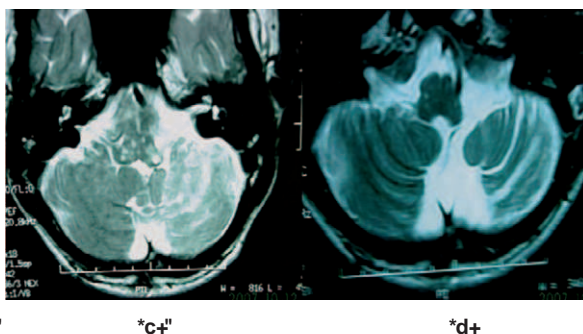




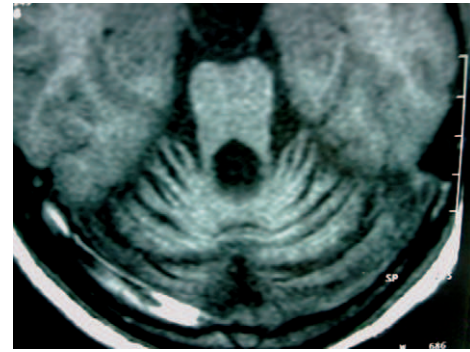
**Fig. 76.8:** PML: A heterogeneous hyperintensity on T2-weighted MRI involving the left parieto-occipital white matter with involvement of the U fibers, splenium of corpus callosum and extending to the right side.

matter (Fig. 76.8), followed by cerebellum, brainstem, corpus callosum, basal ganglia, and rarely the spinal cord. The borders of the lesions are ill-defined and irregularly shaped and grow asymmetrically. Cortical involvement may be seen in up to 10% of cases and in 20% lesions are restricted to the posterior fossa. Subtle enhancement or space-occupying lesion like presentation may be seen in 10% of patients not undergoing immune reconstitution. MRS may reveal a reduced NAA and creatine content with increase in choline and lactate. Magnetization transfer ratios are characteristically lower in PML as opposed to cases of HIV encephalopathy. CSF analysis occasionally reveals pleocytosis and estimation of JC virus DNA PCR is sensitive as well as specific to the diagnosis.

Therapeutic response to cidofovir is partial. A large retrospective study analysis of 35 cases with PML showed a significantly shorter median survival in patients with HAART and cidofovir as compared to HAART only.<sup>55</sup> By far the best therapy of PML in AIDS patients is an optimal antiretroviral



**Fig. 76.9 a, b:** PML with lesions restricted to the posterior fossa before and after HAART: T2 weighted MR image on the left (July 2005) shows well-defined nodular hyperintensities over the medulla and left cerebellar white matter ( $CD4+ = 76/mm^3$ ). Resolution of lesions seen in repeat MRI (Oct 2007) with residual gliosis over the cerebellum ( $CD4+ = 357/mm^3$ ).



**Fig. 76.10:** Probable JC virus granule cell neuronopathy. T1 weighted MRI showing prominence of cerebellar foliae with absence of white matter involvement consistent with cerebellar atrophy. This seropositive patient presented with a progressive pancerebellar syndrome and  $CD4+$  counts of  $72/mm^3$ . Evaluation for alternative causes including for other hereditary degenerative ataxias was negative.

therapy (Fig. 76.9 a,b), significantly lowering HIV-1 RNA viral load in plasma and possibly in CSF and also improving cellular immune function. Many reports of IRIS in patients treated for PML with HAART have surfaced. The syndrome typically begins a few weeks of HAART and is characterized by clinical worsening and progression of previously MRI-defined lesions or development of new lesions, often with enhancement. Both fatal and benign courses are described.<sup>56,57</sup> Some experts suggest anti-inflammatory treatment in such cases with corticosteroids, but this approach is controversial. Looking at one aspect, restoration of immune function is required to clear JC virus and on the other hand fulminant inflammation with progressive neurological deterioration is not preferable.

Poor survival is associated with HIV-1 RNA plasma levels  $>500$  copies/mL and low  $CD4+$  counts  $<100/mm^3$ , JC viral load  $>100$  copies/ $mm^3$ .<sup>58</sup> HLA-A2 positive status is also thought to improve the survival of PML patients.<sup>58</sup>

### Cerebellar Degeneration in HIV-Positive Patient

Development of a subacute to chronic progressive pancerebellar syndrome in a seropositive patient renders a wide differential diagnosis. Possibilities include the following:

- Indirect effects of HIV infection
- Effect of cytokines on cerebellum
- JC virus (JCV) granule cell neuronopathy (Fig. 76.10)
- Toxins
- Alcohol
- Phenytoin
- Mercurial compounds
- Genetic (hereditary cerebellar atrophy)

A novel entity recently described is the JC virus granule cell neuronopathy, which leads to cerebellar atrophy.<sup>59,60</sup> The full-length sequence of a granule cell neuron-tropic JCV variant

(GCN) associated with lytic infection of granule cell neurons and cerebellar atrophy in an HIV-infected patient with PML was determined and compared with the sequence of the JCV isolate from the classic PML lesions present in the hemispheric white matter (HWM) of the same individual. A unique deletion was found in the C terminus of the VP1 gene of JCVGCN1, which encodes the major capsid protein, resulting in a frame shift and a total change of the C-terminal amino acid sequence of this protein. This deletion was not present in JCVHWM, suggesting that this mutation may be instrumental in facilitating entry or replication of JCV into granule cell neurons.

## Primary CNS Lymphoma

This B-cell origin neoplasm is considered to be an opportunistic infection caused by Epstein–Barr virus (EBV). Its incidence appears to be cumulatively rising because of the increased longevity of HIV-infected patients, following the efficacy of both prophylactic and therapeutic measures against OI and early initiation of HAART. The incidence as noted in two Indian series is very low (0.2–1.7%)<sup>3,48</sup> as opposed to 6–18% in Western literature.<sup>61</sup>

Patients present with focal or polyfocal symptoms and signs as in toxoplasmosis and PML. The temporal clinical profile is actually slower than in toxoplasmosis and faster than in PML, with patients presenting several days or a few weeks after the onset of symptoms, which may include headache, hemiparesis, aphasia, ataxia, behavioral changes, and altered mentation.<sup>62</sup> Distinctly, lymphomatous meningitis and ocular dissemination may be evident.

Neuroimaging is sensitive for detection of lesions, which are usually deep, well-circumscribed, subcortical, or subependymal with occasional mass effect and usually little contrast enhancement (Fig. 76.11) or surrounding edema.<sup>62</sup> CSF cytology requires concurrent

flow cytometry for detection of monoclonal B lymphocytes. This may be corroborated by CSF PCR for EBV DNA and brain biopsy. Thallium-201 SPECT may be useful in supporting the diagnosis of PCNSL and prompting early biopsy.

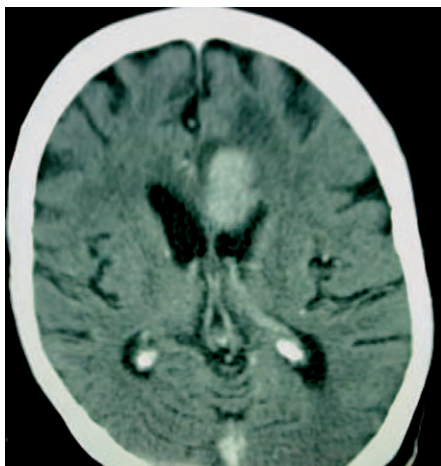
Prior to the era of HAART, a median survival of 2–3 months was seen. The most important factors related to survival include Karnofsky performance status, the CD4+ counts, elevation of CSF protein, and the absence of OI.<sup>63</sup> Prognosis is improved by a good HAART regimen and immune reconstitution, and vigorous attempts to suppress HIV replication are recommended in all patients.<sup>64</sup> Corticosteroids may be administered in case of mass effect. Though use of chemotherapy as recommended in seronegative hosts is limited to clinical trials, palliative whole brain irradiation therapy is recommended.<sup>62</sup>

## Stroke

Focal neurological signs and symptoms may occur due to cerebrovascular disease. Ischemic and hemorrhagic strokes have been reported in up to 4% of clinical series and up to 34% of autopsy series.<sup>65</sup> Association with HIV neuropathology itself is uncertain. HIV-associated thrombocytopenia, hepatic dysfunction and related coagulopathies, disseminated intravascular coagulation, PCNSL, Kaposi sarcoma, and occasionally toxoplasmosis are postulated mechanisms of intracranial hemorrhage. Ischemic stroke mechanisms include meningovascular syphilis, varicella zoster vasculopathy, and subacute bacterial endocarditis, vasculitis including TB vasculitis and procoagulant states. Long term effects of atherosclerosis, lipodystrophy, and metabolic syndrome induced by protease inhibitors are under evaluation. Angioinvasive fungi like aspergillus and mucor may cause strokes. Venous thrombosis may be encountered following dehydration induced by diarrheal illnesses or from thrombophilic states such as lupus anticoagulant.

## Seizures

New onset of seizures occur in 8% of adults and up to 20% of children who have HIV infection, although among patients followed regularly in HIV clinics, the prevalence of seizures is lower.<sup>38</sup> Generalized tonic-clonic seizures that can progress to status epilepticus is the commonest.<sup>66</sup> Toxoplasmosis, tuberculomas, cryptococcal meningitis, and PCNSL are the common causes of focal seizures. Other than OIs, medications, substance use or withdrawal as in alcohol or cocaine use, metabolic states and HIV infection per se may represent common causes of seizures. Drugs such as selective serotonin reuptake inhibitors, tricyclic antidepressants, ganciclovir, and foscarnet can lower the seizure threshold. In up to 50% of HIV-seropositive individuals, no underlying cause of the seizure is found except HIV itself.<sup>67</sup> A significant subset of these patients have a propensity to develop HAD. Because HIV-seropositive patients inherently have an increased rate of adverse drug reactions, up to a quarter of these patients will develop a rash with phenytoin. There is also a



**Fig. 76.11:** Primary CNS lymphoma: Contrast enhanced CT showing a homogeneously enhancing lesion over the left frontal subcortical white matter with juxtaventricular extent.

potential for drug interactions to occur between anticonvulsants and HAART because these groups of drugs are largely metabolized by the cytochrome p450 system. In addition, protease inhibitors competitively bind to albumin, thus altering anticonvulsant drug efficacy. Carbamazepine is however well-tolerated when it is coupled with regular monitoring of anticonvulsant drug levels and viral load.<sup>38</sup> Valproate has been shown to induce viral replication *in vitro*, although this has not been demonstrated *in vivo*.<sup>68</sup> Newer antiepileptic drugs like gabapentin, pregabalin, topiramate, and levetiracetam may be safer. The risks of using “first-line” anticonvulsants (carbamazepine, phenytoin, valproate) appear to be minimal, assuming viral load and anticonvulsant levels are measured regularly as part of ongoing care.

## Headache

Approach to a seropositive patient complaining of headache presents a diagnostic challenge. In view of advanced stages of immunosuppression as commonly encountered, secondary headache merits consideration. Primary headaches such as migraine with/without aura, tension type headaches, despite their higher prevalence in general population, are diagnoses of exclusion. An emergent neuroimaging study may often delineate granulomas, lymphomas, and meningitis. Papilledema may be seen in a large subset, requiring antiedema measures before attempting CSF evaluation in the absence of evident midline shift. Immunosuppressed hosts may not harbor significant pleocytosis, so attempts at isolation of organisms should be contemplated. Granulomatous lesions in the brain may follow chronic infections, e.g., tuberculosis, syphilis, and cryptococcosis. In such a setting, the review of past medical investigations and treatment will be more useful, especially when CSF and radiology are inconclusive and stereotactic biopsy is not feasible.

Management of primary headache disorders is no different from that in the general population. Depression merits consideration in chronic primary headaches, especially in the initial months of detection of seropositive status but as emphasized earlier, it remains a diagnosis of exclusion.

## Other Focal CNS Disorders

Cerebral abscesses may form after dissemination from infected indwelling catheters and in intravenous drug abusers. Other than bacteremia, tuberculous abscess, syphilitic gumma, bartonellosis and nocardiosis merit consideration. Fungal causes are also to be considered in view of angioinvasiveness. Neurocysticercosis may also be encountered. In patients who have travelled to endemic areas, intracerebral Chagas disease needs to be considered. VZV may cause a demyelinating syndrome with lateralizing features, and CMV has been reported to cause mass lesions.<sup>69</sup> It is interesting that HIV infection does not appear to significantly increase the risk for herpes simplex virus encephalitis, though HSV-2 infections may be encountered. Opportunistic infective granulomas in the basal ganglia may lead to extrapyramidal disorders, e.g., choreoathetosis, dystonia, hemiballismus, and

rarely, parkinsonism.<sup>70</sup> Chorea in AIDS has been described in toxoplasmosis, PML, and HIV encephalopathy.<sup>71</sup>

## SPINAL CORD DISORDERS

### HIV-Associated Myelopathy/Vacuolar Myelopathy (VM)

The spinal cord is most commonly affected in HIV infection. VM is unusual in the early stages of HIV disease but is relatively common in advanced infection. Autopsy studies have identified white matter changes in 20–55% of patients although clinical myelopathy is less common.<sup>72</sup>

VM affects 5–10% of untreated AIDS-defined patients, usually manifesting as gait ataxia, leg weakness, spasticity, and incontinence.<sup>73</sup> Impaired proprioception with sensory ataxia may also be seen as in subacute combined degeneration of cord or tabes dorsalis. Onset and progression is fairly insidious, with no back pain. Upper limb signs are less common, although hyper reflexia in the arms may occasionally be seen. There is no sensory level. Subclinical VM may be evident in otherwise asymptomatic patients with features such as hyper reflexia, spasticity, and extensor plantar response.

In the differential diagnosis for HIV-associated myelopathy, clinicians should exclude other treatable conditions that could cause spinal cord disease, particularly compressive lesions and other infectious or neoplastic etiologies. Conditions such as HTLV type I and II infection, vitamin B<sub>12</sub> deficiency, multiple sclerosis, varicella zoster associated myelopathy can present with similar features. Pott spine, intramedullary tuberculomas, toxoplasmosis, syphilis, and acute transverse myelitis also need to be considered. The most common mass lesion affecting the spinal cord is lymphoma. It may present as a compressive lesion, meningeal lymphomatosis or as epidural metastases. HIV-infected intravenous drug users may develop spinal epidural abscess caused by *S. aureus*, which is a neurosurgical emergency. Atypical mycobacteria, *M. avium* complex may also rarely cause spinal epidural abscess with presacral and piriformis muscle inflammation.<sup>74</sup> Cryptococcal myelitis with or without vertebral osteomyelitis has also been described.<sup>75</sup>

Tests such as complete blood counts with indices, vitamin B<sub>12</sub> levels and neuroimaging studies should be performed to rule out other and treatable causes of chronic myelopathies. Investigations such as serum RPR or VDRL, toxoplasma antibodies, cryptococcal antigen also need to be obtained. The neuropathologic correlates of VM are axonal injury and intense macrophage infiltration, which is found in over 50% of HIV/AIDS at autopsy. The vacuolar appearance primarily localized in the lateral and dorsal columns of thoracic spinal cord may reflect intramyelinic edema.<sup>76</sup>

Although HAART appears to reduce the incidence of VM, limited reversal of the signs or symptoms is observed after therapy is implemented. Symptomatic treatment (including baclofen and gabapentin) for painful spasticity, neurogenic bladder, clonus, and tremor is frequently beneficial to patients who have VM.



## NEUROPATHIES

HIV-1 infection is associated with a wide variety of peripheral neuropathy syndromes, with onset from the time of seroconversion to the late stages of AIDS.<sup>77,78</sup>

### Acute and Chronic Inflammatory Demyelinating Polyradiculoneuropathies

AIDP often occurs early in the course of HIV infection, particularly during seroconversion. It causes rapidly progressive weakness, with minor sensory symptoms and generalized areflexia. CIDP symptoms and signs are similar to acute IDP, except that CIDP is more slowly progressive (>6 weeks), has a more protracted course, and may be monophasic or relapsing. Blood studies should include serum lactate and bicarbonate to screen for hyperlactatemia. CSF analysis usually reveals elevated protein level with evidence of lymphocytic pleocytosis (10–50 cells/mm<sup>3</sup>) as opposed to seronegative patients where the characteristic albumino-cytological dissociation is evident. CSF-CMV PCR should be determined. Electrophysiological findings are consistent with demyelination. Plasmapheresis or intravenous immunoglobulin (IVIgG) is the preferred treatment for both acute and chronic inflammatory demyelinating polyneuropathies if the illness is sufficiently severe to warrant intervention.

### Mononeuropathy Multiplex

Mononeuropathy multiplex is relatively rare. It is characterized clinically by multifocal motor and sensory nerve abnormalities. These abnormalities have an asymmetric distribution. Tendon reflexes are preserved in uninvolved areas. Extensive nerve involvement may rapidly progress to include multiple cranial nerves. The occurrence is bimodal with the first peak at CD4+ >200 cell/mm<sup>3</sup> and the second peak at CD4+ 50–100 cells/mm<sup>3</sup>. It may be associated with herpes zoster, CMV, hepatitis C, syphilis, lymphomatous infiltration, or necrotizing vasculitis. Unilateral or bilateral facial palsy may accompany HIV-1 seroconversion. In those with CD4+ of <200, CMV infection is to be ruled out. If not demonstrated peripheral nerve vasculitis needs to be considered. Nerve biopsy studies reveal that Schwann cells may be infected directly by HIV-1 particles.<sup>79</sup> It is preferable to observe patients with early-onset MM because it may spontaneously resolve within weeks to several months. HAART may be initiated in patients with late-onset MM occurring in advanced HIV infection. In cases of delayed or incomplete recovery, corticosteroids, plasmapheresis, or IVIgG may be indicated.

### Progressive Polyradiculoneuropathy

This occurs most commonly in advanced HIV infection when CD4 cell counts decrease to <50 cells/mm<sup>3</sup>. Rapid onset of radiating pain and paresthesias in a cauda equina distribution followed by signs of progressive involvement of multiple nerve roots, usually lumbar and sacral is seen. Clinical signs include

flaccid paraparesis, sphincter dysfunction, and lower extremity areflexia. With the advent of HAART its incidence, particularly polyradiculopathy due to CMV, has markedly decreased. Contrast-enhanced MRI of the lumbar spine may reveal increased T2 signal of cauda equina and enhanced, thickened, and clumped lumbosacral roots. CSF is to be assayed for CMV, VZV, VDRL, and cytology. In CMV polyradiculopathy, CSF shows marked polymorphonuclear pleocytosis (>40% cells), elevated protein and hypoglycorrhachia. For most of the other etiologies mentioned, CSF reveals predominantly lymphocytic pleocytosis. EMG studies show reduced number of motor units and abnormal spontaneous activity in weak muscles. Nerve conduction velocities are only mildly abnormal. Prompt initiation of anti-CMV therapy may lead to improvement of symptoms or stabilization of signs in progressive polyradiculopathy secondary to CMV. Optimization of HAART in patients with progressive polyradiculopathy is necessary. Polyradiculoneuropathy secondary to CMV has 100% mortality when effective antiviral treatment is not given. Combination therapy with ganciclovir and foscarnet may provide efficacy, but no controlled data are available to support this.

Another condition associated with HIV-1 infection, diffuse infiltrative lymphocytosis syndrome, is a nonmalignant CD8 lymphocytosis that may affect multiple viscera as well as peripheral nerve and may respond to either corticosteroid or HAART.<sup>80</sup> Herpes zoster radiculitis can lead to ataxic sensory polyganglionopathy during seroconversion.

### HIV1-Associated Motor Neuron Disease (MND)

A retrospective review of 1700 cases of HIV-1 infected patients identified 6 cases presenting as a reversible ALS-like syndrome.<sup>81</sup> Younger age of onset (<40 years) was noted with a characteristic monomelic presentation involving adjoining segments of one limb followed by rapid spread. There were clinical features of both upper and lower motor neuron involvement. Rapidly progressive dementia was also noted in two patients. CSF was inconclusive while MRI revealed diffuse white matter signal intensities consistent with HAD. Electrophysiology revealed a widespread motor axonopathy. In each case HAART was beneficial in stabilizing the disease and in two cases curing it.

### Distal Sensory Polyneuropathy (DSP)

In advanced stages of AIDS, 25–38% of patients suffer from DSP.<sup>82</sup> DSP may occur secondary to HIV (HIV-DSP) or may be due to antiretroviral (ARV) drug toxicity (ARV-DSP). The clinical features of HIV-DSP and ARV-DSP are identical, with pain and paresthesias being the principal symptoms. Timely detection may allow for the reversal of the toxic effects of ARVs and for the initiation of symptomatic treatment.

The pathogenic mechanism of HIV-DSP is uncertain but likely multifactorial.<sup>83</sup> HIV-DSP tends to appear in advanced stages of HIV infection. It is thought that HIV disease progression

leads to dysregulation of macrophages and overproduction of proinflammatory cytokines and chemokines, which in turn leads to DSP. ARV-DSP is associated with the use of the NRTIs didanosine (ddI), zalcitabine (ddC), and stavudine (d4T). More recently, some protease inhibitors (PIs), including indinavir, saquinavir, and ritonavir, have also been implicated. These ARVs appear to have adverse effects on metabolism, with increased risk for mitochondrial toxicity. In many cases, ARV toxicity may unmask a previously asymptomatic HIV-DSP or may act synergistically with the pathogenic effect of HIV itself. Exacerbation by concomitant diabetes mellitus, alcoholism is often evident. The pathologic hallmark is distal axonal degeneration. Small-diameter nociceptive sensory axons and their respective soma in the dorsal root ganglion are the principal cellular structures affected.

Patients typically present with paresthesias, dysesthesias, and/or numbness in “stocking and glove” distribution and reduced deep tendon reflexes. Loss of proprioception and significant objective muscle weakness are atypical for DSP. ARV-DSP usually bears a temporal relationship to initiation of the drug. A history of symptom onset soon after the initiation of a potentially neurotoxic ARV, often within weeks, supports the diagnosis of ARV-DSP. Most important, symptoms improve or resolve within 8 weeks following dose reduction or drug cessation, although in some patients, a “coasting phenomenon” of increased symptoms may follow drug discontinuation before clinical improvement occurs. Incomplete resolution of symptoms and signs following cessation of neurotoxic drugs may be due to coexistent HIV-DSP. Patients who have any systemic polyneuropathy, including HIV- and ARV-DSP, may be at higher risk for superimposed entrapment neuropathies.

Blood studies should be performed to exclude other causes of DSP (e.g., glucose,  $B_{12}$ ). Electrophysiological studies reveal absence or reduction of sural nerve amplitudes. Nerve biopsy is rarely necessary in DSP, except in atypical cases. Skin biopsy with epidermal nerve fiber density studies is currently used in the research setting.<sup>84</sup>

The approach to treatment of DSP begins with eliminating neurotoxic ARVs when possible. In cases of ARV therapy-associated DSP, the decision to discontinue a neurotoxic ARV drug is not automatic and should only be made after carefully weighing the risks and benefits of virologic control versus neuropathic symptom control. Any coexisting risk factors identified during the patient's evaluation, such as other neurotoxic medications, diabetes mellitus, or impaired glucose tolerance, vitamin  $B_{12}$  deficiency, renal or liver impairment, thyroid dysfunction, or syphilis, should be addressed. Mild analgesics, including acetaminophen, aspirin, or other NSAIDs, with or without adjunctive agents (e.g., anticonvulsants, antidepressants, topical agents), are the first line of therapy for pain control. Successful treatment of pain requires combinations of therapies that have different mechanisms of action, an approach termed rational polypharmacy.<sup>85</sup> Experimental therapies include peptide T, acetyl-L-carnitine, recombinant human nerve growth factor and erythropoietin. Tricyclic antidepressants (TCAs) and

selective serotonin-norepinephrine reuptake inhibitors (SNRIs) are the two major classes of antidepressants used in the treatment of neuropathic pain. Because TCAs may cause sedation and other anticholinergic side effects, they are typically started as a single low evening dose, such as amitriptyline (10–25 mg), and titrated to efficacy as tolerated. Two agents of the SNRI class are available: duloxetine and venlafaxine. Duloxetine is generally well-tolerated. The most common side effect of duloxetine (nausea) can be ameliorated by starting treatment at 30 mg daily and increasing to the recommended dose of 60 mg daily up to 120 mg daily after approximately 1 week. Anticonvulsants used include pregabalin (75–300 mg/day) and gabapentin (600–2400 mg/day). The vanilloid receptor agonist capsaicin interacts with C-fiber polymodal nociceptors. Epidermal nerve fibers have been shown to be capsaicin sensitive nociceptors. A 30- to 90-minute application of high-dose topical capsaicin patch, approximately once every 3 months, has shown significant pain relief in HIV-DSP.<sup>86</sup> Side effects include mild irritation, erythema, or burning pain at the application site. Mild opiates such as low-dose codeine, hydrocodone, and propoxyphene, usually in combination with NSAIDs, are used for moderate pain; more potent opioids including morphine, oxycodone, fentanyl, and methadone are used for severe pain.<sup>87</sup> There has been recent interest in more rapid-onset treatments for breakthrough pain in chronic pain syndromes such as HIV-DSP. Recent data show efficacy for an oral effervescent form of fentanyl in several forms of neuropathic pain.<sup>88</sup>

## MYOPATHY

Myopathic symptoms can arise from toxic (zidovudine) or dysimmune (polymyositis) causes or from AIDS cachexia (muscle wasting syndrome).<sup>89</sup> HIV-associated myopathy or polymyositis presents with slowly progressive weakness of proximal muscles and myalgias. Neurological examination reveals symmetric weakness of proximal muscles of the extremities and neck flexors. Deep tendon reflexes are intact unless there is superimposed peripheral neuropathy or myelopathy. On occasion it may be associated with immune restoration during HAART.<sup>90</sup> CPK levels are usually elevated (approx. 500 U/mL). Electromyography shows muscle irritability with abnormal spontaneous activity and myopathic features. Muscle biopsy reveals myofiber atrophy, often with associated endomysial inflammatory infiltrates. HIV does not appear to directly infect muscle fibers, but rather induces them to express major histocompatibility complex I, triggering cell-mediated muscle fiber injury. Inclusion body myositis has also been reported.<sup>89</sup> Although corticosteroids may provide benefit in HIV myopathy, they should be used with caution because of their immunosuppressant effects. Intravenous immunoglobulin is an alternative. Some patients with myopathy improve when zidovudine or other nucleoside ARV drugs are discontinued, but most do not.

HIV-associated neuromuscular weakness syndrome (HANWS) is commonly associated with the use of d4T. It is characterized by progressive weakness that develops over days to weeks and

may progress to respiratory failure and death.<sup>91</sup> Lactic acidosis or hyperlactatemia is often present. Electrophysiologic studies reveal axonal neuropathy or myopathy. Other common peripheral neuropathies associated with comorbidities also need to be excluded, including diabetes mellitus, hypothyroidism, nutritional deficiency, excess ethanol consumption, hepatitis B or C virus or syphilis infections, and other drug-related conditions.

Zidovudine myopathy is due to mitochondrial toxicity,<sup>92</sup> especially in doses of >1000 mg/day on monotherapy or lesser doses on HAART. At least 6 months of exposure to the drug is necessary. Proximal weakness and myalgia are presenting features. Clinical response to a drug holiday or reduction in dose often obviates the need for biopsy.

Pyomyositis can present as a focal suppurative myositis with fever, local muscle pain and swelling and bacteremia.<sup>93</sup> It is commonly caused by *Staph. aureus*, *Salmonella spp.* or gram-negative bacilli. Surgical drainage followed by intravenous antibiotics for 1–2 weeks and then oral therapy for up to 8 weeks is necessary. Disseminated infection with *Cryptococcus*, *Toxoplasma*, *M. tuberculosis*, *M. avium intracellulare*, and microsporidia may also involve muscle.

## Neurologic Immune Reconstitution Inflammatory Syndrome (IRIS)

As immunologic improvement begins with suppression of the viral load in blood and as the patient's CD4+ T cell count rises, the clinical deterioration occurs, usually within weeks of ART initiation, although IRIS has been recognized months after ART was started. The mechanism of clinical deterioration during IRIS is thought to be sudden activation and increase in CD4 T cells (specifically CD45RO memory cells), resulting in a heightened immune response and significant host-mediated inflammatory cell damage.<sup>94</sup> The onset of neurologic signs and symptoms or worsening of prior neurologic disabilities is often apparent in patients who have very low CD4 T-cell counts and concurrent CNS opportunistic infections<sup>95</sup> after HAART is introduced; this syndrome is termed neurologic IRIS (neuro IRIS). The underlying opportunistic infection may be active, although in some cases, it is subclinical and does not manifest itself until after HAART is initiated.<sup>96</sup> Across most studies,<sup>97</sup> approximately 20–25% of patients started on cART develop some form of IRIS, whereas the risk of neuro IRIS is substantially lower. On average, 60% of patients who develop IRIS present within 60 days of initiating cART, although its presentation can be biphasic, with onset within 30 days of initiating cART or after 90 days.<sup>98</sup> Neuro IRIS results in focal CNS deficits including encephalopathy, hemiparesis and seizures, CSF pleocytosis, and white matter and cortical abnormalities in neuroimaging, and is frequently observed in the context of pre-existing progressive multifocal leukoencephalopathy, cryptococcal meningitis, cytomegalovirus retinitis, and occasionally HAD. Neuropathologic studies of neuro IRIS disclose widespread leukocyte (lymphocyte and macrophage) infiltrates in the brain, frequently proximate to the pre-existing infection.<sup>99,100</sup> The extent of neurologic disability varies widely but may respond to treatment with glucocorticoids,

although the full extent of neuro IRIS in terms of epidemiology and underlying pathogenesis warrants further study.

## Conclusions

More than half of HIV-infected patients develop symptomatic neurological disease. The nervous system is extensively involved with no part of the neuraxis being immune from the virus. Neurological complications typically occur with advanced disease and profound immunosuppression.<sup>101</sup> Since many of the conditions are amenable to treatment, a proper diagnosis and therapy may decrease morbidity in the already curtailed life span of the patient. The aim of the physician should be to unmask the neurological disorder from a host of symptoms keeping in mind that there is “layering” or “parallel tracking” of various etiologies in HIV neurology.

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## Introduction

Gastrointestinal and hepatobiliary symptoms are among the most frequent complaints in patients with human immunodeficiency virus (HIV) infection and AIDS, developing anytime during the course of the illness. These include a wide-spectrum of illnesses, some caused by HIV itself but more often caused by opportunistic infections and neoplasms. They present difficult diagnostic and management challenges to the treating physicians, who may have to use their acumen and a wide battery of laboratory investigations to identify the vast number of potential infections, neoplasms, and consequences of treatment of HIV. Involvement of different organs of gastrointestinal tract in HIV-infected individuals is discussed below.

## Oropharyngeal Manifestations

Oropharyngeal manifestations are common in patients with HIV infection. They cause significant morbidity and also provide diagnostic clues to the underlying immunocompromised status. These may be a reason for referral and investigation for HIV infection.<sup>1-5</sup> Oral pathologies can occur in up to 80% patients infected with HIV. The most common complaint is thrush (oropharyngeal candidiasis). It may be an early indication of a suppressed immune status, but is not a good predictor of the severity of immunosuppression. It typically appears as white curd like patches or as an atrophic white or red friable lesion on the mucosal surface.<sup>1-5</sup> It is only a modest predictor of underlying esophageal candidiasis. Oral candidiasis is subdivided into the following categories: pseudomembranous candidiasis (thrush), erythematous candidiasis, angular cheilitis, and hyperplastic candidiasis (leukoplakia).<sup>1-5</sup> Pseudomembranous candidiasis is the most commonly recognized form and is characterized by whitish plaques throughout the oral cavity. The erythematous form presents as reddish lesions on the palate or dorsum of the tongue. Angular cheilitis is recognized as red, flaking lesions at the corners of mouth. Hyperplastic candidiasis is the least common presentation in HIV infection and is characterized by easily identified thick, white plaques on mucosa. The diagnosis is frequently made on clinical grounds but confirmation can be

achieved by demonstration of pseudohyphae on KOH smears. Topical treatment with nystatin (100,000 IU Tab 3–5/day) or clotrimazole (10 mg troches/lozenges) is generally effective. In patients with associated esophageal candidiasis, systemic treatment with fluconazole (100–200 mg daily for 7–14 days) is preferable. The problem is one of frequent recurrences and need for repeated courses of treatment.

Individuals infected with HIV commonly develop oropharyngeal ulcers. The prevalence has been suggested to be around 10%.<sup>2-5</sup> Possible causes include (i) viruses such as herpes simplex virus (HSV), reactivated varicella zoster virus, and cytomegalovirus (CMV); (ii) immunologic causes such as aphthous ulcers; and less commonly (iii) fungal infections such as histoplasmosis.<sup>4-9</sup> Herpes simplex and dermatomal varicella zoster reactivation (shingles), commonly involve the perioral skin and sometimes the oral mucosa also. They present as small, very painful vesicles and ulcers. Cytomegalovirus and aphthous ulcers may appear similar to varicella zoster and HSV infection clinically, but both lack a prodrome. Cytomegalovirus is distinguished by the presence of intranuclear or intracytoplasmic inclusions seen on microscopic analysis. Confirmation can be obtained with immunohistochemistry.<sup>9-10</sup> Histoplasmosis lesions begin as flat, nontender plaques that then evolve to painful ulcers. Scraping of the lesions for fungal culture is helpful to confirm the diagnosis.

Other oral lesions associated with HIV infection include neoplastic growths such as human papillomavirus (HPV) infection, lesions of Kaposi sarcoma, and lymphomas.<sup>9-18</sup> HPV infection may present as condyloma acuminata, or focal epithelial hyperplasia. Simple surgical excision is usually curative.

The prevalence of oral hairy leukoplakia (OHL) has been found to range from 18% to 23% in HIV-infected patients.<sup>2-4</sup> It appears as corrugated white lesions almost always on the lateral borders of the tongue. It is usually asymptomatic and may appear early in the course of the illness, but there is no correlation with stage of the disease. Confirmation by histopathological examination is required for the diagnosis and oral candidiasis is to be ruled out. The presence of oral hairy leukoplakia is a



harbinger for disease progression; 48% of patients with oral hairy leukoplakia develop AIDS diagnosis within 16 months, and 83% develop an AIDS diagnosis within 31 months. As it is usually asymptomatic, treatment is empirical or elective and includes acyclovir, topical retinoic acid, and local application of podophyllin.

Although Kaposi sarcoma more commonly presents on the skin, the hard palate, gingiva, buccal mucosa, dorsum of tongue, and nasal mucosa can be involved. Mucosal Kaposi sarcoma appears as a red to purple raised plaque, which can ulcerate. More frequently than cutaneous Kaposi sarcoma, mucosal Kaposi sarcoma presents with pain, ulceration, and bleeding.<sup>5-9</sup> Mucosal Kaposi sarcoma is usually accompanied by concurrent cutaneous lesions. Treatment focusses on local control of symptoms and may include excision, external-beam radiation, and vinblastine injection.

Other conditions include recurrent aphthous ulcerations, chronic mucocutaneous HSV infection and bartonellosis. Severe periodontal disease and alveolar bone loss is also frequent. Drug reactions and Stevens–Johnson syndrome have become more frequent with the advent of antiretroviral drugs.

## Esophageal Disorders

Esophageal symptoms occur in one-third of the patients with AIDS. Esophagitis is associated with a poor prognosis, with untreated patients having a mean survival time of 5 months.<sup>1-6</sup> The most common symptoms of esophageal disease include odynophagia, dysphagia, and retrosternal chest pain. The presence of a particular symptom is not indicative of any specific etiology although infection with candida is most common.<sup>2-6</sup> Other symptoms include bleeding from the ulcer(s), coughing, and aspiration from the bronchoesophageal fistula.<sup>6-9</sup> Esophageal disease can be divided broadly into three etiologic groups: infections, neoplasms, and others noninfectious, non-neoplastic causes.

### INFECTIONS

Candida is the most common esophageal pathogen in AIDS, followed by viral diseases.<sup>1-6</sup> In the era of highly active antiretroviral therapy (HAART), many of the previously common HIV-related infectious disorders have essentially vanished. Nevertheless, these opportunistic disorders can be observed in patients who are failing HAART (low CD4, high viral load) or who are noncompliant.

Patients with a CD4 count <200 cells/mL are those at greatest risk for opportunistic infections (Table 77.1). Also, the risk of candidiasis rises exponentially with a fall in CD4 cells <100 cells/ $\mu$ L. Candida esophagitis rises in incidence at a CD4 count of 100–200  $\mu$ L, whereas *Mycobacterium avium* complex is very uncommon until the CD4 count falls below 50.

### Candida Albicans

Candida is the most frequent cause of fungal esophagitis occurring in 42–79% of patients.<sup>1-6</sup> In the immunocompromised patient, colonization becomes more widespread and may be followed by

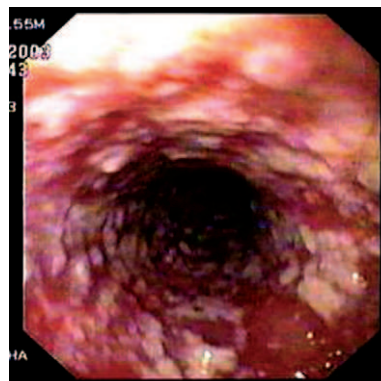
**Table 77.1:** Correlation of CD4 Cell Count and Gastrointestinal Infection

CD4 cell count	Common infections
CD4 <50 cells/ $\mu$ L	<i>Mycobacterium avium</i> complex Cryptococcus <i>Penicillium marneffei</i> Cytomegalovirus
CD4 <100 cells/ $\mu$ L	Cryptosporidium species Microsporidium species <i>Leishmania donovani</i>
CD4 <250 cells/ $\mu$ L	<i>Histoplasma capsulatum</i> <i>Coccidioides immitis</i>
At any level of CD4 cell count	<i>Clostridium difficile</i> Salmonella Shigella <i>Campylobacter jejuni</i> <i>Isospora belli</i> <i>Mycobacterium tuberculosis</i> <i>Cyclospora cayetanensis</i> <i>Strongyloides stercoralis</i> <i>Ancylostoma duodenale</i>

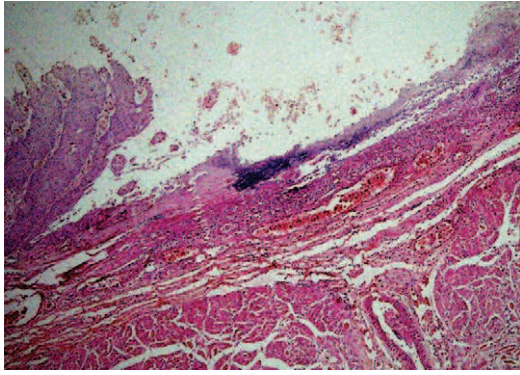
epithelial or deeper invasion into the mucosa and submucosa.<sup>2-6</sup> Endoscopic appearance is characterized by creamy yellowish white plaques overlying erythematous base (Fig. 77.1a,b,c). Plaque removal may reveal underlying erosion and mucosal friability. Other fungi causing esophagitis include *Torulopsis glabrata*, *Histoplasma capsulatum*, and *Aspergillus*.

### Cytomegalovirus (CMV)

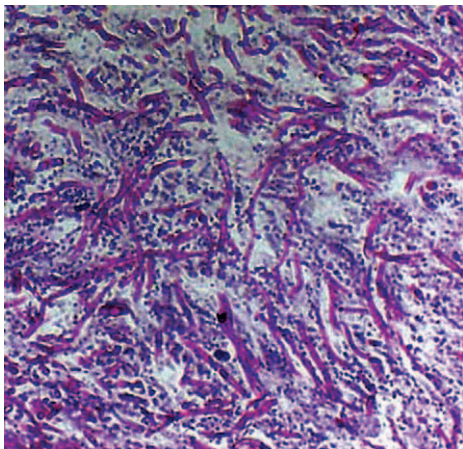
It is the most common viral infection accounting for 45% of all esophageal ulcers on endoscopy in HIV-positive patients.<sup>2-9</sup> It is almost always associated with odynophagia and CD4 counts are usually less than 120 cells/ $\mu$ L. The majority of the CMV lesions are located in the middle (57%) and distal third (32%) of the esophagus. Ulcers are usually greater than 1 cm in size (giant esophageal ulcers), and in another 28% of cases they are greater than 2 cm.<sup>9,10</sup> In 8% of the patients, the ulcers may be deep, and in about 58% patients they may be multiple. Lesions may also



**Fig. 77.1a:** Yellowish-white plaques of Candida esophagitis at endoscopy.



**Fig. 77.1b :** Low power photomicrograph of an esophageal biopsy showing a deep mucosal ulcer with necrotic ulcer bed (H&E,  $\times 45$ ). *Courtesy:* Dr. Kim Vaiphei, Professor of Pathology, PGIMER, Chandigarh.



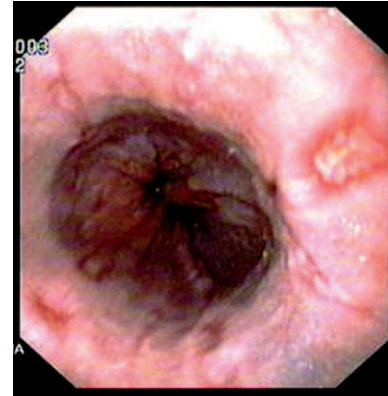
**Fig. 77.1c:** High power photomicrograph of the same to show multiple fungal pseudohyphae and budding yeasts of *Candida*, seen in bright magenta color (PAS,  $\times 450$ ). *Courtesy:* Dr. Kim Vaiphei, Professor of Pathology, PGIMER, Chandigarh.

appear as heaped up ulcers and/or as large exophytic lesions. Complications include strictures and bacterial superinfection.<sup>9–11</sup>

As CMV infects stromal cells, multiple biopsies must be taken from the center of the ulcer. The diagnosis of gastrointestinal CMV infection is best established by demonstrating viral cytopathic effect in tissue specimens. The inclusions may be atypical in appearance or few in number, requiring immunostaining and/or *in situ* hybridization for confirmation. Biopsies can also be subjected to viral culture or PCR.

### Herpes Simplex Virus (HSV)

It is a common infection found when CD4<sup>+</sup> count is 150 cells/ $\mu$ L or less. The complaints include dysphagia (86%), odynophagia (82%), chest pain (68%), fever (44%), nausea, vomiting, and rarely hematemesis.<sup>13–20</sup> Associated herpetic



**Fig. 77.2:** Endoscopic picture of HSV esophagitis.

lesions on the nasolabial region may suggest the diagnosis in a patient presenting with dysphagia and odynophagia. The earliest lesions are 1–3 mm rounded vesicles in the middle to distal esophagus, which slough and form small discrete punched out (volcano) ulcers. Later, the ulcers coalesce and develop an overlying white or yellow pseudomembrane, mucosal friability, and plaque formation (Fig. 77.2). Complications include mucosal necrosis and super-infection, hemorrhage, stricture, HSV pneumonia, tracheoesophageal fistula, hiccups, and disseminated HSV.<sup>13–20</sup>

Staining of HSV-infected epithelial cells demonstrate multinucleated giant cells, ballooning degeneration, “ground glass” intranuclear Cowdry type A inclusion bodies, and margination of chromatin. Immunohistochemical staining may make the diagnosis of HSV in tissues easier. HSV may be cultured from esophageal tissue which may also be subjected to PCR; both are more sensitive than routine histology or cytology.

Herpes esophagitis can be treated with a 7–10-day course of orally administered acyclovir or valacyclovir. With severe odynophagia or in very sick patients, treatment can be started with intravenous acyclovir, 250 mg/m<sup>2</sup> every 8 hours and then changing to oral therapy when the patient can take oral medication.

### HIV

Whether or not the presence of HIV-infected cells in the alimentary tract leads to symptoms is debatable. In patients with esophageal symptoms, HIV-1 mRNA was detected in 36% of the patients. Esophageal ulcers are found during seroconversion, with a finding of randomly distributed single or multiple ulcers, which are round or oval 3–15 mm in diameter with distinct margins and surrounding normal mucosa.<sup>15–20</sup> These clinical and pathologic findings resolve over a period of 2 weeks.

### Mycobacteria

Mycobacteria including *M. tuberculosis* and *M. avium* complex can cause diffuse irregularity of the mucosa, mucosal ulcers, sinus tracts, and tracheoesophageal and esophagobronchial fistulae.<sup>6</sup>

## NEOPLASTIC DISEASES

Neoplastic diseases are highly unusual in the esophagus in patients with AIDS. The most common neoplasm of the esophagus is Kaposi sarcoma, seen in 16% of the patients.

## NONINFECTIOUS, NON-NEOPLASTIC CAUSES OF ESOPHAGEAL LESIONS

### Drug-Induced Esophagitis

Patients are at risk for pill induced esophagitis due to the numerous drugs that they take and many have an underlying motility disorder.<sup>19</sup> The offending drugs include doxycycline, potassium preparations, NSAIDs, zidovudine, and zalcitabine. Gastroesophageal reflux (GER) disease is quite uncommon in this group as many patients have achlorhydria.

### Idiopathic Esophageal (Aphthous) Ulcers

This term describes ulcers in HIV-infected individuals in whom no cause is identified despite a thorough histopathological examination of the tissue. The clinical picture is one of odynophagia, substernal chest pain, and little or no relief with narcotics or analgesics. Average CD4 counts are usually <50 cells/ $\mu$ L.<sup>9</sup> Giant esophageal ulcers are common.<sup>9</sup> The postulated mechanism is overproduction of cytokines, especially interleukin (IL)-1, IL-6, and arachidonic acid metabolites. This is evidenced by a good response to thalidomide 200 mg/day which inhibits cytokine tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and also inhibits angiogenesis.<sup>20,21</sup>

## MANAGEMENT OF ESOPHAGEAL DISEASES

Recent data have suggested a role for empirical use of fluconazole 100 mg PO for 7 days in patients with mild to moderate symptoms of recent onset. It results in improvement in 78% of the patients, as *Candida* is the most common organism found in this subset of patients.<sup>20,21</sup> Patients with severe symptoms, (e.g., inability to eat), or with a suspected complication, (such as a fistula) should undergo early endoscopy and biopsy. Such patients should be treated with 400 mg/day of fluconazole. Recurrent esophageal candidiasis is almost universal; however, long-term prophylaxis is expensive and carries the risk of resistance.<sup>22-24</sup>

Cytomegalovirus responds to either ganciclovir or foscarnet (response rate 85% vs. 83%), but both are ineffective in preventing recurrences. Regardless of the regimen used, relapse occurs in 39% of complete responders not on maintenance therapy.<sup>23,24</sup> Herpetic esophagitis responds to acyclovir at a dose of 15–30 mg/kg/day IV/orally. Valacyclovir and famciclovir are preferred by some because of less frequent dosing and better absorption.<sup>22-24</sup> Prednisolone in a dose of 40 mg/day and tapered by 10 mg/week has been tried for idiopathic aphthous and esophageal ulcers. One promising new therapy for this is thalidomide 200 mg daily for 2 weeks.<sup>21,24</sup>

## Gastroduodenal Diseases

Gastroduodenal ulcers are infrequent in HIV-positive subjects.<sup>25-28</sup> CMV is the only organism significantly associated with gastroduodenal ulcerations, and *Helicobacter pylori* is an uncommon cause of ulcers.<sup>24</sup> Chronic active gastritis is more common and is associated with pathogens other than *H. pylori*.<sup>24</sup> This also explains the low prevalence of low-grade gastric mucosa associated lymphoid tissue (MALT) lymphomas in HIV-positive patients.<sup>25</sup> Hypochlorhydria is common and occurs early in the course of HIV disease. Abnormal secretory function of the parietal cells affects acid as well as intrinsic factor secretion. It is associated with morphological changes in acid secretory apparatus.<sup>26,27</sup> HIV-associated visceral neuropathy may be present in the relatively late stages of infection and may contribute to abdominal symptoms like dyspepsia, dysphagia, vomiting, and nausea that frequently occur in these individuals. This is evidenced by faster gastric emptying rate of liquids and significantly delayed emptying of solids.<sup>26-28</sup>

## Diarrheal Diseases

Diarrhea is one of the most common manifestations of HIV infection. Substantial diarrhea occurs in about 50% of the HIV-infected individuals in developed countries and the corresponding figure for developing and underdeveloped countries may be as high as 80%.<sup>29-34</sup> The most common cause of diarrhea in this population remains opportunistic infections but the rate of isolation of a specific pathogen depends on the extent of diagnostic work up carried out on these patients.<sup>32-36</sup> With exhaustive and intuitive evaluation, specific enteric pathogens can be isolated in most patients with severe diarrhea. Diarrhea leads to a diminished quality of life. Clinical presentation of HIV-associated diarrhea depends on the principal area of the gut involved. Small-bowel type of diarrhea tends to produce large, bulky, postprandial stools. These patients commonly have postprandial periumbilical pain and significant weight loss. In contrast, predominant large bowel involvement results in more frequent but small volume stools which may contain visible amounts of blood and mucus. Dehydration is uncommon with only large bowel type of diarrhea and location of pain, if present, is lower abdomen. Chronic diarrhea is an independent marker of poor prognosis in patients with AIDS.

### CAUSES OF DIARRHEAL ILLNESSES (TABLE 77.2)

A definite cause for diarrhea can be identified in 50–80% of patients with AIDS. In the remaining 20%, no clear cause is evident.<sup>30-36</sup> The other proposed mechanisms include direct effect of HIV, altered intestinal permeability, bile acid malabsorption, dysregulation of enteric immune system, local production of lymphokines, and autoimmune denervation.<sup>30-36</sup>

In the era of HAART, opportunistic infections causing diarrhea have fallen dramatically.<sup>30-34</sup> Experience at a single center between

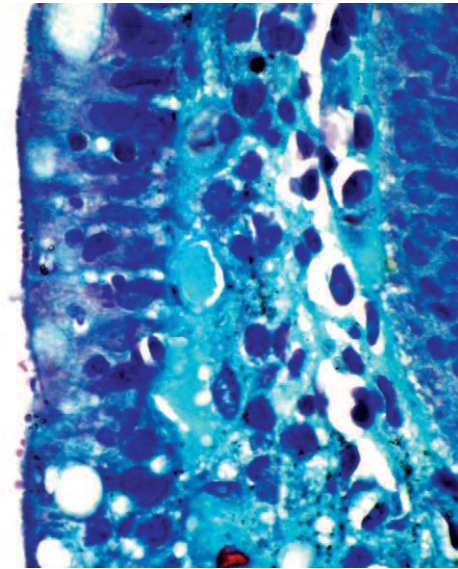


**Table 77.2:** Causes of Diarrhea in HIV-infected Patients

Small intestine
<ul style="list-style-type: none"> <li>• <i>Cryptosporidium</i></li> <li>• Microsporidia</li> <li>• <i>Isospora belli</i></li> <li>• <i>Cyclospora cayentanensis</i></li> <li>• <i>Mycobacterium avium</i> complex</li> <li>• <i>Histoplasma capsulatum</i></li> <li>• <i>Salmonella</i> spp.</li> <li>• <i>Campylobacter</i> spp.</li> <li>• <i>Giardia lamblia</i></li> <li>• HIV</li> </ul>
Large intestine
<ul style="list-style-type: none"> <li>• Cytomegalovirus</li> <li>• <i>Cryptosporidium</i></li> <li>• <i>Mycobacterium avium</i> complex</li> <li>• Shigella group</li> <li>• <i>Clostridium difficile</i></li> <li>• <i>Campylobacter</i> spp.</li> <li>• <i>Escherichia coli</i></li> <li>• <i>Entamoeba histolytica</i></li> <li>• <i>Histoplasma capsulatum</i></li> <li>• Adenovirus</li> <li>• <i>Pneumocystis jiroveci</i> (rare)</li> <li>• Herpes simplex virus</li> <li>• HIV</li> </ul>
Miscellaneous
<ul style="list-style-type: none"> <li>• Drugs</li> <li>• Lactose intolerance</li> <li>• Pancreatitis</li> <li>• Kaposi sarcoma</li> <li>• Non-Hodgkin lymphoma (NHL)</li> </ul>

1995 and 1997 found that the occurrence of chronic diarrhea remained constant (8–10% per year) for those with CD4 counts <200 cells/ $\mu$ L. Opportunistic infections with HAART fell drastically from 53% to 13%, while other infections unrelated to immunodeficiency rose.<sup>30–33</sup> The proportion of patients diagnosed with noninfectious causes increased from 32% to 70% over the 3-year period. Diarrhea may be caused by a number of drugs in the patients infected with HIV. Drug-induced diarrhea has been frequently attributed to protease inhibitors, and studies suggest that diarrhea occurs in up to 50% of patients taking nelfinavir and in up to 20% of those taking lopinavir/ritonavir and fosamprenavir/ritonavir.<sup>36–39</sup> Often there is a temporal association between drug initiation and diarrhea, and typically diarrhea is of mild to moderate severity.

A search for typical HIV-associated processes should be undertaken based upon risk stratification of the patient. Patients with severe immunodeficiency (CD4 count  $\leq$ 100 cells/ $\mu$ L) are those most at risk for cryptosporidium, microsporidium, and CMV disease. *Mycobacterium avium* complex, commonly seen in the pre-HAART era, is now very rare and is most likely to be found in the patient who first presents with end-stage HIV infection. *Mycobacterium tuberculosis* can involve the gut and is an important cause of disease in AIDS patients in the developing world. The same is true for *Giardia lamblia* (Fig. 77.3).



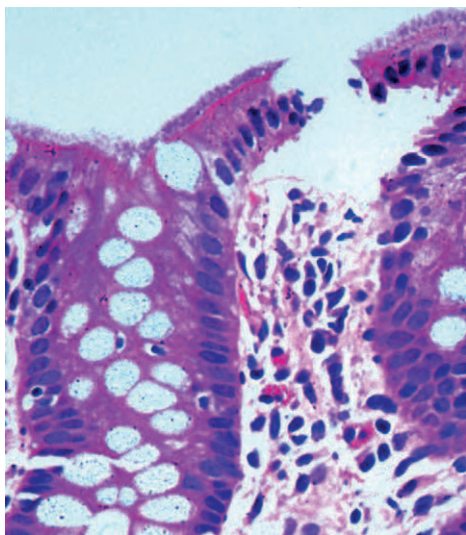
**Fig. 77.3:** Photomicrograph of duodenal biopsy from a patient who presented with chronic diarrhea showing intact surface epithelium with clusters of pear to sickle shaped *Giardia lamblia* trophozoites (H&E,  $\times$ 450). Courtesy: Dr. Kim Vaiphei, Professor of Pathology, PGIMER, Chandigarh.

## Specific Infections

### CRYPTOSPORIDIUM

*Cryptosporidium parvum* is the species that infects both humans and cattle. The modes of transmission are water contamination and direct feco-oral route. *Cryptosporidium parvum* primarily inhabits the microvillous border of intestinal epithelial cells. Its oocysts are highly environmentally resistant. As cell-mediated immunity declines to CD4 count less than 180 cells/mL, patients develop chronic, heavy cryptosporidial infection.<sup>30–33,39–41</sup> The ileum and jejunum are primary sites of infection with vitamin B12, and d-xylose malabsorption occurring due to villous atrophy and altered permeability.

In immunocompetent persons, cryptosporidiosis is a self-limited diarrheal illness with an incubation period of 7 days and a mean duration of 12 days. In immunodeficient HIV-infected individuals, however, infection may be prolonged. The diarrhea is non-bloody and may be associated with nausea, vomiting, and abdominal cramps. Patients with CD4 cell count of >180/ $\mu$ L tend to clear the infection. Four patterns of infection have been described among the HIV-infected patients: (i) asymptomatic (4% of patients); (ii) transient symptomatic (28%), which spontaneously resolved within 2 months; (iii) chronic (60%), which persisted for at least 2 months; and (iv) fulminant (8%), which was refractory to therapy and was characterized by the passage of 2 liters or more of liquid stool daily.<sup>30–33,39–41</sup> Biliary and respiratory tract involvement can occur in advanced AIDS. Biliary manifestations include acalculous cholecystitis, sclerosing cholangitis, or pancreatitis, which usually presents with right upper quadrant abdominal pain.



**Fig. 77.4:** Photomicrograph of duodenal biopsy from a patient with long standing small bowel diarrhea showing mild inflammation of the lining epithelium with many small spherical bodies seen as reddish structures (cryptosporidia) on Masson trichrome staining ( $\times 450$ ). Courtesy: Dr. Kim Vaiphei, Professor of Pathology, PGIMER, Chandigarh.

Cryptosporidial oocysts can be shown in stool samples using either a modified acid-fast stain or a commercially available kit based on an immunofluorescence technique. The organism can also be detected using light-microscopic examination of duodenal (Fig. 77.4) or, less commonly, colonic mucosal biopsy specimens. Diagnosis is by stool examination using modified acid-fast stain and microscopy or enzyme-linked immunosorbent assay (ELISA).

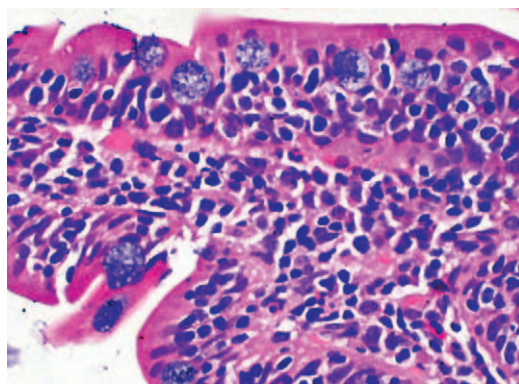
Nitazoxanide and paromomycin are the two drugs which have been shown to be effective in treatment of diarrhea caused by cryptosporidium. In clinical trials, overall 59% of patients treated with nitazoxanide achieved a clinical response with culture-negative stools while on nitazoxanide therapy; patients with higher CD4 counts were more likely to achieve a continued clinical response.<sup>30–33,40–48</sup> Variable response rate has been reported with paromomycin. Paromomycin might result in some clinical improvement in patients with cryptosporidial diarrhea, but these improvements were short lived and associated with a high relapse rate, approaching 33% once therapy was discontinued. There is paucity of data comparing the efficacy of nitazoxanide and paromomycin. Current evidence strongly supports the use of HAART as initial therapy for patients with cryptosporidiosis; HAART clearly has shown consistent clinical effects and the ability to cure parasitic infections in many HIV-infected patients. For patients who continue to have severe diarrheal disease despite HAART and improved CD4+ T-cell function, the addition of nitazoxanide therapy should be considered. However, nitazoxanide therapy alone is inappropriate without HAART.<sup>30–33,39–41</sup>

Other agents tried includes clarithromycin, octreotide, atovaquone, spiramycin, bovine dialyzable leukocyte extract, and bovine hyperimmune colostrums and rifaximin either as single agent or in various combinations but the published experience is very limited and efficacy usually limited and variable.

## MICROSPORIDIA

These are obligate intracellular spore producing microorganisms, now classified as fungus, that commonly cause chronic diarrhea, malabsorption, and wasting. *Encephalitozoon intestinalis* and *Enterocytozoon bieneusi* are the two most prevalent species encountered in immunocompromised patients. About 90% infections are due to *Enterocytozoon bieneusi*, which is found in 15–34% of AIDS patients with chronic diarrhea.<sup>30–33,49–57</sup> Symptomatic patients have CD4+ cell counts less than 100 cells/ $\mu$ L and present with multiple nonbloody, nonmucoid stools, abdominal discomfort, and occasionally vomiting but no fever. The infection is greatest in proximal jejunum resulting in villous atrophy and crypt hyperplasia leading to malabsorption. The organisms are round, 1–2 micron in diameter and are seen on duodenal biopsies with modified trichrome stain and fluorochrome calcofluor (Fig. 77.5). They are present at the apical cytoplasm of the villous enterocytes and contain prominent clefts.<sup>49–57</sup>

Antiretroviral therapy is of paramount importance in treating HIV patients who have microsporidium infections. HAART alone can result in cessation of diarrhea, considerable weight gain in wasting patients, and even a complete eradication of the organism. *Encephalitozoon intestinalis* infection consistently responds to albendazole. Albendazole inhibits tubulin polymerization and may even result in complete eradication of *Encephalitozoon intestinalis* infection in HIV-positive patients. In contrast, treatment of *Enterocytozoon bieneusi* infection is more difficult and challenging. Albendazole has limited efficacy against *Enterocytozoon bieneusi*.



**Fig. 77.5:** Photomicrograph of the duodenal biopsy showing crypts with mild increase in intraepithelial lymphocytes of the lining epithelial cells. The goblet cells are seen containing small round to oval uniform size hematoxyphilic bodies of Microsporidium (H&E,  $\times 450$ ). Courtesy: Dr. Kim Vaiphei, Professor of Pathology, PGIMER, Chandigarh.



infection and suppression is often incomplete and inconsistent. Fumagillin, an antibiotic with antiangiogenic properties, showed encouraging results in early studies in improving HIV symptoms and fecal clearance of the organism. A host of other agents have been tried, mostly with limited success. These agents include nitazoxanide, atovaquone, itraconazole, metronidazole, octreotide, thalidomide, and trimethoprim/sulfamethoxazole.

### ISOSPORA BELLI

It is clinically associated with less severe diarrhea. The prolonged gastrointestinal disease caused by it resembles mild cryptosporidiosis. It invades the proximal small intestine. The diarrhea is profuse, watery, nonbloody, and is associated with abdominal cramping.<sup>30–33</sup> On intestinal biopsy, acid-fast oocysts, measuring 20–30 micron, are seen within the bowel lumen or in cytoplasmic vacuoles in enterocytes with surrounding inflammation.<sup>54–57</sup>

Trimethoprim/sulfamethoxazole (160/800 mg) given orally 4 times a day for 10 days is the currently preferred initial therapy for this condition.<sup>30–33</sup> Although the initial response rate is fair, but relapses are common, particularly among the patients for whom HAART cannot be started or when CD4+ T-cell counts continue to remain less than 200 cells/ $\mu$ L. Due to high recurrence rate, secondary prophylaxis may be required, especially among the subjects who continue to have CD4 cell count <200 cells/ $\mu$ L. Ciprofloxacin nitazoxanide and pyrimethamine are the other agents which are useful in the treatment of this condition.

### CYCLOSPORA CAYETANENSIS

It is an acid-fast coccidian seen in AIDS patients when the CD4 counts decline to less than 50 cells/ $\mu$ L.<sup>30–37</sup> It causes prolonged watery diarrhea, anorexia, fatigue, nausea, bloating, and weight loss. There may be involvement of biliary tract. Cyclospora is seen as acid-fast, round oocysts, 9–10 micron in diameter as nonrefractile hyaline spheres containing globular inclusions in unstained smears.<sup>54–57</sup> The other protozoa seen, more in homosexual individuals, are *Entamoeba histolytica*, *Giardia lamblia*, and *Blastocystis hominis*.<sup>48</sup>

Treatment of cyclospora infection, including the indications for starting secondary prophylaxis is similar to isospora infection. The preferred therapy for cyclospora infection is trimethoprim/sulfamethoxazole (160/800 mg) orally 4 times a day for 7 days. Ciprofloxacin and nitazoxanide are the other useful drugs to treat this infection but their efficacy may be lower. Secondary prophylaxis may be required in those with very low CD4 cell count.

### CYTOMEGALOVIRUS

In patients with HIV infection, the source of CMV disease is either reactivation or reinfection because most individuals have been previously exposed to the virus. In a cohort study of patients with AIDS or symptomatic HIV infection followed up for 2 years, the cumulative probability of developing CMV disease was 21% for those with initial CD4 counts of 100/ $\mu$ L or less. Nearly 15%

of CMV infections occur in the GI tract and the prevalence of CMV colitis in HIV patients with diarrhea ranges from 13% to 45%.<sup>30–33,58–62</sup> CMV disease may involve any site of GIT, but it most often affects the small and large intestines but can also cause duodenal ulcers, enteritis, and ileocaecal perforation.<sup>30–33,61,62</sup> It is a major cause of morbidity and mortality in immunocompromised patients. Most patients experience intermittent or persistent diarrhea, cramping, lower abdominal pain, tenesmus, and weight loss. Patients are often febrile reflecting the invasive nature of the disease and also have anorexia, malaise, and rebound tenderness. It can also present as massive lower gastrointestinal bleed and pseudotumoral mucosal lesions. The possible mechanism of enteritis is CMV-induced vasculitis leading to thrombosis and occlusion of submucosal vessels causing ischemia. Clinical CMV disease occurs when the CD4 counts decline to less than 100/ $\mu$ L. As colitis progresses, full thickness of the bowel wall ulcerates and ultimately perforates. This and obstruction of the gut due to CMV is responsible for one-third of all abdominal surgeries required in AIDS patients.<sup>59–60</sup> On endoscopy, the mucosa is diffusely erythematous and friable with submucosal hemorrhages and mucosal ulcerations (Fig. 77.6a,b). Ulcers are discrete, round, or serpiginous and have a clean base. In one study, 41% had localized

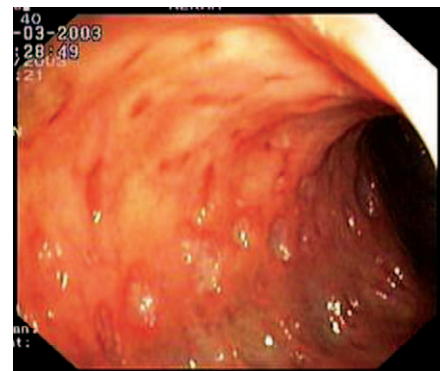


Fig. 77.6a: Colonoscopic view of CMV colitis.

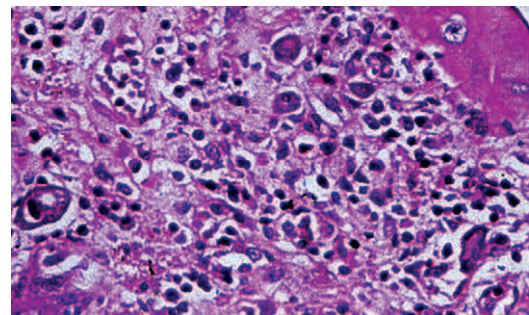


Fig. 77.6b: Photomicrograph of colonic biopsy colitis showing a part of atrophic surface epithelium with granulation tissue underneath. Many cytomegaly cells are seen interspersed with other inflammatory cells. Some of the cytomegaly cells have with intra-nuclear inclusion surrounded by a clear hallow around. (H&E,  $\times 450$ ). Courtesy: Dr. Kim Vaiphei, Professor of Pathology, PGIMER, Chandigarh.



patchy colitis, 34% had diffuse colitis, and 25% had normal mucosa.<sup>62</sup> There is a high percentage of right colonic disease, which highlights the importance of performing colonoscopy and taking biopsy samples from ascending, transverse, and descending colon. On hematoxylin and eosin (H&E) stain, characteristic changes include eosinophilic intracytoplasmic inclusion bodies surrounded by clear halos.

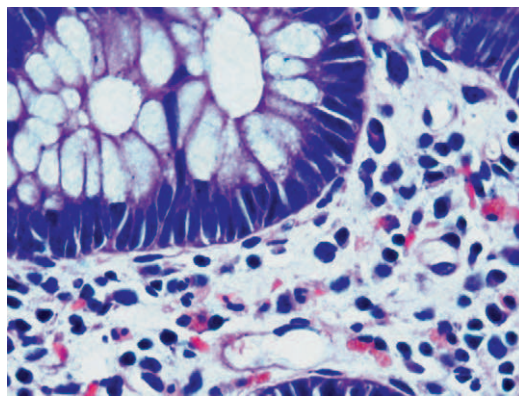
CMV infection of the GI tract should be treated with either ganciclovir or foscarnet for 3–6 weeks.<sup>30–33,37,38</sup> Duration of therapy can vary and depends on clinical resolution of signs and symptoms. Another emerging option to this essentially parenteral therapy is oral valganciclovir unless symptoms prevent a patient from taking oral medications and/or if symptoms are severe enough to result in intestinal malabsorption and thus decrease drug bioavailability. Both ganciclovir and foscarnet have been shown to lead to improvement in clinical symptoms, resolution of endoscopic findings, and disappearance of inclusion bodies on biopsy. Role of maintenance therapy remains uncertain and benefits in the setting of CMV infection of GIT have not been clearly defined. However, maintenance therapy may be considered if patients continue to have symptoms despite a complete course of therapy or if a patient has recurring disease. The need for maintenance therapy may be negated with the introduction of HAART. The appropriate time for initiating HAART in patients with GI CMV disease is a source of controversy. Given the theoretical risk of developing immune reconstitution syndrome many clinicians advocate delaying HAART until the acute symptoms of disease resolve with CMV therapy. Conversely, some clinicians argue that starting HAART alone in patients with mild to moderate CMV GI disease is a safe and reasonable first step rather than initially starting with directed CMV therapy. However, the available data does not favor one therapeutic strategy over the other.

## ADENOVIRUS

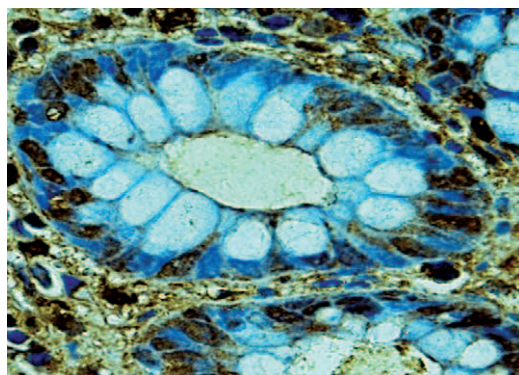
Gastrointestinal adenovirus excretion occurs at an advanced stage of HIV disease and is associated with a poor prognosis.<sup>64–68</sup> It is seen when CD4+ lymphocyte count is less than 200/ $\mu$ L. Adenovirus has been linked to “pathogen-negative” persistent diarrhea in patients with a characteristic colitis. Adenovirus infected cells show characteristic amphophilic or eosinophilic nuclear inclusions, predominantly affecting the surface epithelium and characteristically involving the goblet cells.

## HERPES SIMPLEX AND VARICELLA ZOSTER VIRUSES

Herpes simplex is frequently associated with proctitis or distal colitis and may result in mild diarrheal illness or even constipation.<sup>63–68</sup> Small vesicles are seen on the colonic mucosa that rupture to form small rounded ulcers and may coalesce to form a large ulcer. Histologically typical inclusion bodies are seen (Fig. 77.7a,b). Gastrointestinal complications of herpes zoster are very rare, with most cases showing only temporal or



**Fig. 77.7a:** Photomicrograph of colonic biopsy showing crypt epithelial lining with enlarged nuclei, many of the nuclei show intranuclear reddish irregular inclusions (H&E,  $\times 450$ ).



**Fig. 77.7b:** Photomicrograph of the same biopsy showing a positive staining of many intranuclear inclusions stained brown color in immunostained section (PAP,  $\times 450$ ).

radiological evidence. It can also present as pseudo-obstruction and toxic megacolon.

## FUNGAL INFECTIONS

The most common organism is *Histoplasma capsulatum* especially disseminated, with 75% having gastrointestinal involvement.<sup>36</sup> *Candida* colitis is generally asymptomatic but it may occasionally produce discrete ulcers resembling viral disease.<sup>36,62</sup>

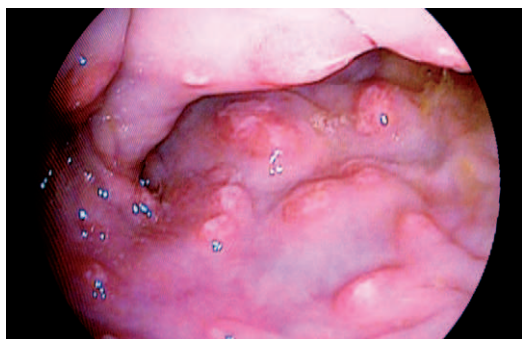
## BACTERIAL INFECTIONS

Salmonella (*S. typhimurium*, *S. enteritidis*), Shigella (*S. flexneri*, *S. dysenteriae*, *S. sonnei*), and *Campylobacter jejuni* have a high incidence of diarrheal disease among the immunocompromised and represent significant pathogens in HIV disease.<sup>36</sup> *Mycobacterium avium* complex (MAC) infection is seen when CD4+ counts decline to less than 50 cells/ $\mu$ L. Diarrheal illness is typically protracted and associated with abdominal pain, anorexia, fever, weight loss, anemia, and night sweats.<sup>36,44</sup> Complications include obstruction, fistula formation, bleeding, and perforation.<sup>59</sup> Endoscopically, MAC infection appears as granular white nodules 2–4 mm in diameter with surrounding erythema.

Initial, first-line treatment for MAC consists of two antibiotics: clarithromycin and ethambutol. Each agent alone has high rates of drug resistance, whereas a combination of the two results in complete microbiologic response, lower relapse rates, improved clinical symptoms, and overall better survival. Rifabutin is another antibiotic effective against MAC and can be added to the regimen to counter problem of resistance and some resultant increased efficacy. Some guidelines have recommended addition of either injectable amikacin or streptomycin to therapy for patients at high risk of death from MAC, which include patients with CD4 T-cell counts of 50 cells/ $\mu$ L or less, high mycobacterial load, or in the absence of HAART. MAC treatment is lifelong or until immune function has improved with HAART.

Human intestinal spirochetosis is a condition defined by the presence of a layer of spirochetes attached by one end to the colorectal epithelium. The pathologic significance is uncertain, but it has been associated with chronic diarrhea and abdominal complaints in HIV-positive patients.<sup>69</sup> Two anaerobic species, *Brachyspira pilosicoli* and *Brachyspira aalborgi*, are commonly implicated.<sup>69</sup>

*Clostridium difficile* has been implicated as the causative organism in 10–25% of patients who have antibiotic-associated diarrhea, in 50–75% of those who have antibiotic-associated colitis, and in 90–100% of those who have antibiotic-associated pseudomembranous colitis.<sup>70–72</sup> In those who acquire *Clostridium difficile*, the immune status of the host is an important determinant of the outcome. Patients who have more severe underlying illnesses are more likely to develop symptomatic disease. The clinical presentation of *Clostridium difficile* colitis is variable. Some individuals who even have toxigenic strains in stool remain asymptomatic. Patients who have symptoms can have disease that can range from diarrhea, colitis without pseudomembranes, pseudomembranous colitis, to fulminant colitis. Some patients have disease primarily in the cecum and right colon, presenting with marked leukocytosis and abdominal pain but little or no diarrhea. Colonoscopic features for pseudomembranous colitis are pathognomonic for this disease. On endoscopy, the colonic mucosa is studded with adherent raised yellowish plaques that can easily be dislodged (Fig. 77.8). Pseudomembranes tend to be most pronounced in the rectosigmoid area. The main prerequisite



**Fig. 77.8:** Colonoscopic view—exudative lesions of *C. difficile* colitis.

for *Clostridium difficile*-associated disease is antibiotic usage. Other risk factors that have been described include: degree of severity of underlying illness, use of proton pump inhibitors, gastrointestinal surgery, older patient age, prolonged hospital stay, stay in the ICU, and tube feeding.<sup>70–72</sup>

The cell cytotoxicity assay has been regarded as the “gold standard” for the diagnosis of *Clostridium difficile* infection. It is a labor-intensive process, and results take up to 48–72 hours. Various EIAs are commercially available that use monoclonal antibodies to toxin A, toxins A and B together, or the other common antigen (glutamate dehydrogenase). These tests are easy to use, and are much less costly. Polymerase chain reaction amplification of toxin B gene for diagnosis of *Clostridium difficile* infection is also commercially available. Recommendations for treating *Clostridium difficile* colitis include discontinuation of antibiotics, supportive nonspecific therapy, and addition of metronidazole for those who fail to respond within 2–3 days. Oral vancomycin was recommended for patients (i) who were critically ill, unable to tolerate metronidazole, pregnant, or younger than 10 years; (ii) who failed initial therapy with metronidazole; or (iii) whose organism proved to be metronidazole resistant. Doses of vancomycin ranging from 125 to 500 mg 4 times daily were found to be equally effective. A randomized trial comparing metronidazole and vancomycin in 92 patients for 10 days noted similar rates of response (88% for vancomycin and 90% for metronidazole) and recurrence (12% for vancomycin and 5% for metronidazole) within a 21-day follow-up period.<sup>70–72</sup> Other agents which have been used successfully in the treatment of this condition include bacitracin, teicoplanin, fusidic acid, nitazoxanide, rifaximin, and probiotics.

## HIV Enteropathy

HIV may be transported through the M cells directly to the mucosal lymphoid follicles. Alternatively, it may infect enterocytes via Fc receptor (by antibody bound HIV) or via CD4 independent receptor (by successive budding on the basal side) to reach the lamina propria. In addition, these changes may be responsible for the partial small intestinal mucosal atrophy and maturational defects seen in these patients. In 20% HIV-positive patients with diarrheal illness, no cause is found. These cases are labeled as HIV enteropathy or HIV colitis.<sup>73–79</sup> The HIV is seen in the mononuclear cells of lamina propria in 30–39% of patients with AIDS. Depletion and functional impairment of the mucosal CD4+ cells with altered cytokine secretion may explain the breakdown of mucosal barrier leading to secondary opportunistic or nonopportunistic infections and secondary malignancies.<sup>73–79</sup>

## EVALUATION OF A PATIENT WITH DIARRHEAL ILLNESS (TABLE 77.3)

Routine stool testing is reasonable depending on the suspected cause and duration (acute vs. chronic) of symptoms and has a yield of 13–75% depending on the epidemiological setting, CD4 count, and number of stool tests performed.<sup>30,34,37–39</sup> In

**Table 77.3:** Diagnostic Work Up for Evaluation of Diarrhea in HIV-positive Patients

- Bacterial culture (to detect *Salmonella* species, *Shigella* species, etc.)
- Ova and parasite examination
- *C. difficile* toxin assay
- Modified acid-fast stain or immunofluorescence kit (cryptosporidia)
- Modified trichrome stain (microsporidia)
- Blood culture in febrile patients
- Flexible sigmoidoscopy/colonoscopy with mucosal biopsies from abnormal looking area
  - Light microscopy (mycobacteria, CMV, cryptosporidia, etc.)
  - Mycobacterial culture
  - PCR for tuberculosis and other agents
- Upper endoscopy and biopsies from abnormal looking areas
  - Light microscopy (giardia, strongyloides, CMV, mycobacteria, cryptosporidia)
  - Mycobacterial culture
  - PCR sample for various agents

many cases, no infectious agent can be identified as the cause of gastrointestinal abnormality. Specific diagnosis depends on stool studies and invasive methods like endoscopic examination of gastrointestinal tract. Analysis of duodenal/bile juice is a simple, rapid, and effective method, which increases the yield of detection of enteral pathogens. Special histological stains for fungal, mycobacterial, and viral infections do not increase the diagnostic yield but add to the cost.<sup>63</sup> For patients with CD4+ cell counts less than 100/ $\mu$ L and AIDS-related unexplained diarrhea, flexible sigmoidoscopy with biopsy is desirable.

Prospective studies have shown a high yield of endoscopic examination with biopsy of the lower and upper GI tract in patients with negative stool tests, with a diagnosis established in 65–82%.<sup>30,34,37–39</sup> For those with complaints referable to the distal colon (bright red rectal bleeding, tenesmus, urgency), examination of the distal bowel will often establish the diagnosis, with CMV being the most common cause found. However, one study suggested that CMV colitis may be limited to the right colon in a third of patients, supporting the use of full colonoscopy if the distal colon is endoscopically normal.<sup>30–33,37,38</sup>

## TREATMENT OF DIARRHEAL DISEASE

Recommended regimens for diarrheal diseases in AIDS are given in Table 77.4.<sup>30</sup> Since the introduction of HAART, the prevalence of HIV-related opportunistic infections has significantly decreased in developed countries.<sup>30,34–37</sup> Diarrheal diseases due to opportunistic pathogens are less common than before. Control of HIV replication and immunodeficiency by HAART offers new therapeutic options in cryptosporidiosis and microsporidiosis.

## General or Nonspecific Measures in HIV-Infected Patients with Diarrhea

### Highly Active Antiretroviral Therapy (HAART)

HAART can reduce the patients' load of HIV to a great extent, many times even to an undetectable range.<sup>30,33–40</sup> This may stop further destruction of CD4 lymphocytes and results in

improvement in the degree of immunosuppression. The course of diarrheal disease may be dramatically altered in many, but not all, patients who are compliant with treatment. The benefits of HAART on treating gastrointestinal opportunistic infections are unquestionable and it should be part of the therapy of most gastrointestinal opportunistic infections. However, timing of starting HAART needs to be decided judiciously. Electrolyte imbalance, dehydration, and malnutrition should be corrected, at least to some extent, before starting HAART. Some of the antiretroviral agents, in particular the protease inhibitors such as nelfinavir, fosamprenavir, and ritonavir, are well-known to cause diarrhea. Initiation of HAART may result in immune reconstitution syndrome, and some patients may have temporary worsening of their gastrointestinal or diarrheal symptoms

### Antimotility Agents

Antimotility agents (loperamide, diphenoxylate, codeine) decrease stool output by decreasing GI motility and increase transit time, thus generally promoting fluid and electrolyte absorption. They are somewhat helpful in alleviating the symptoms of mild to moderate diarrhea.

### Adsorbent Drugs

Adsorbents like bismuth subsalicylate and kaolin/pectin are widely used and may be somewhat helpful in treating mild to moderate diarrhea, particularly in pathogen negative group.

### Octreotide

Many clinical studies have evaluated octreotide in patients with AIDS-related diarrhea. The overall clinical response rates to subcutaneous octreotide range from 25% to 40% in most studies. The usual dose is 100–300  $\mu$ g given subcutaneously 3 times a day. Response rate may be better in pathogen negative cases of diarrhea.

## Liver Diseases

Liver disease in patients with HIV and AIDS presents with varied symptoms including fever, right upper quadrant pain, and hepatomegaly. Almost 90% of patients have abnormalities of the liver enzymes at presentation, while 60–73% have enlarged liver.<sup>80–86</sup> Various causes of liver diseases in HIV/AIDS patients are listed in Table 77.5.

## HEPATITIS C VIRUS AND HIV/AIDS

HIV-induced immunosuppression may increase replication of HCV, leading to higher HCV RNA levels and accelerated progression to chronic HCV infection.<sup>80–87</sup> An individual may become infected with multiple strains of HCV and more virulent subtypes may predominate. HCV infection induces CD4+ stimulation, which may increase HIV replication, although it does not increase the severity of HIV infection. There is widespread expression of inducible nitric oxide (NO) synthase in the hepatocytes in chronic HCV liver disease, irrespective of



**Table 77.4:** Preferred Treatment of Specific Pathogens Causing Diarrhea in Subjects Infected with HIV<sup>30</sup>

Pathogen	Preferred therapy
Cryptosporidia	Combination antiretroviral therapy along with any of the following <ul style="list-style-type: none"> <li>Nitazoxanide 500–1000 mg PO bid for 2 weeks</li> <li>Paromomycin 25–35 mg/kg PO daily for 2 weeks</li> <li>Paromomycin 1 g PO bid/Azithromycin 600 mg PO daily for 4 weeks</li> </ul>
<i>Cyclospora cayentanensis</i>	Trimethoprim/sulfamethoxazole 160/800 mg PO qid for 1 week Alternatives – any of the following <ul style="list-style-type: none"> <li>Ciprofloxacin 500 mg PO bid for 1 week</li> <li>Nitazoxanide 500 mg PO bid for 3 days</li> </ul>
<i>Isoospora belli</i>	Trimethoprim/sulfamethoxazole 160/800 mg PO qid for 10 days Alternatives – any of the following <ul style="list-style-type: none"> <li>Ciprofloxacin 500 mg PO bid for 7 days</li> <li>Nitazoxanide 500 mg PO bid for 3 days</li> <li>Pyrimethamine 50–75 mg PO daily for 3–4 weeks</li> </ul>
Microsporidia <i>Encephalitozoon intestinalis</i>	Combination antiretroviral therapy and Albendazole 400 mg PO bid for 2 weeks
Microsporidia <i>Enterocytozoon bienersi</i>	Combination antiretroviral therapy Fumagillin 60 mg PO daily for 2 weeks
Cryptococcus	Initial phase: Amphotericin B deoxycholate 0.7 mg/kg IV daily (or liposomal amphotericin B 4–6 mg/kg IV daily) and Flucytosine 25 mg/kg PO qid for 2 weeks Continuation phase: Fluconazole 400 mg PO daily for 8 weeks
Cytomegalovirus	Combination antiretroviral therapy with any of the following <ul style="list-style-type: none"> <li>Ganciclovir 5 mg/kg IV bid for 3–6 weeks</li> <li>Foscarnet 90 mg/kg IV bid for 3–6 weeks</li> <li>Valganciclovir 900 mg PO bid for 3–4 weeks</li> </ul>
MAC	Clarithromycin 500 mg PO bid Ethambutol 15 mg/kg PO daily (with or without Rifabutin 300 mg PO daily) for 12 weeks
<i>Mycobacterium tuberculosis</i>	Initial phase: All of the following for 2 months <ul style="list-style-type: none"> <li>Isoniazid 5 mg/kg PO daily</li> <li>Rifampicin 10 mg/kg PO</li> <li>Pyrazinamide 15–30 mg/kg PO daily</li> <li>Ethambutol 15–25 mg/kg PO daily</li> </ul> Continuation phase: All of the following for 6 months <ul style="list-style-type: none"> <li>Isoniazid 5 mg/kg PO daily</li> <li>Rifampicin 10 mg/kg PO</li> </ul> See NIH/CDC/HIVMA/IDSA/RNTCP guidelines for details
<i>Campylobacter jejuni</i>	Ciprofloxacin 500 mg PO bid for 1–2 weeks OR Azithromycin 500 mg PO daily for 1–2 weeks
Salmonella	Ciprofloxacin 500–750 mg PO bid for 1–6 weeks OR Trimethoprim/sulfamethoxazole 160/800 mg PO bid for 1–6 weeks
Shigella	Ciprofloxacin 500 mg PO bid for 1–2 weeks OR Trimethoprim/sulfamethoxazole 160/800 mg PO bid for 1 week or Azithromycin 500 mg PO on day 1, then 250 mg PO daily for 4 days

stage of liver disease. However, elevated NO levels in the serum are related only to active AIDS related bacterial, protozoal, and fungal infections, rather than to chronic viral infection with HCV or HIV alone. It may play a role in the local control of chronic viral infection at the tissue level. The responsiveness of these patients to drugs is also reduced. Antiretrovirals may slow the progression of HIV and modulate the presumed HIV/HCV interaction. The response to interferon is seen in only 25% of the patients. The immune improvement seen with protease inhibitor regimens helps reduce HCV load.

HCV, HIV, and hepatitis B virus (HBV) share similar routes of parenteral transmission, which include exposures to infected blood or blood products, sexual transmission among heterosexuals and men who have sex with men, and vertical transmission from an infected mother to her neonate during childbirth. The prevalence of chronic hepatitis C infection in patients with HIV has been reported to be in the range of 25–30%.<sup>80–87</sup> The prevalence, however, is substantially higher in HIV-infected injection drug users, and may be more than 85% but coinfection among persons with sexual transmission as the only risk factor

**Table 77.5:** Causes of Liver Disease in Patients Infected with HIV

<b>Hepatitis</b>
<ul style="list-style-type: none"> <li>• Hepatitis A, B, C, D</li> <li>• Cytomegalovirus</li> <li>• Epstein–Barr virus</li> <li>• Herpes simplex virus</li> <li>• Varicella zoster virus</li> <li>• HIV</li> <li>• Ethanol, hepatotoxic drugs</li> </ul>
<b>Granulomatous infections</b>
<ul style="list-style-type: none"> <li>• <i>Mycobacterium tuberculosis</i></li> <li>• <i>M. avium intracellulare</i></li> <li>• Other atypical mycobacteria</li> </ul>
<b>Fungal</b>
<ul style="list-style-type: none"> <li>• <i>Histoplasma capsulatum</i></li> <li>• <i>Cryptococcus neoformans</i></li> <li>• <i>Coccidioides immitis</i></li> <li>• <i>Candida albicans</i></li> </ul>
<b>Protozoal</b>
<ul style="list-style-type: none"> <li>• <i>P. jiroveci</i></li> <li>• <i>T. gondii</i></li> <li>• Microsporidia</li> <li>• <i>Cryptosporidium parvum</i></li> <li>• <i>Schistosoma</i></li> <li>• <i>E. histolytica</i></li> </ul>
<b>Hepatotoxic drugs</b>
<b>Mass lesions</b>
<ul style="list-style-type: none"> <li>• Kaposi</li> <li>• Non-Hodgkin lymphoma</li> </ul>
<b>Vascular lesions</b>
<ul style="list-style-type: none"> <li>• Peliosis</li> <li>• Kaposi</li> </ul>

is less than 10%. The available data suggests that majority of the coinfecting individuals acquire HIV after having been already infected with HCV. However, it is important to note that a person infected with HIV who later becomes infected with HCV is much less likely to clear the acute HCV infection spontaneously. Whereas 14–45% of patients with acute HCV mono-infections immunologically clear HCV within 6 months, only about 5% of patients with HIV infection spontaneously clear an acute HCV infection, and those with lower CD4 cell counts do so even less frequently. In addition, liver disease appears to progress more quickly to advanced fibrosis and cirrhosis in patients with HCV-HIV coinfection. Approximately 6% of HIV-positive persons fail to develop HCV antibodies; therefore, HCV RNA should be assessed in HIV-positive persons with unexplained liver disease who are anti-HCV negative. However, there is no validated evidence that HCV co-infection significantly alters the natural history of HIV infection.

It is now clear that HIV infection has a detrimental impact on the natural history of HCV infection. Prior to the use of HAART, patients infected with HIV succumbed to AIDS-related complications rather rapidly. With the advent of HAART, however, HIV infections became controllable. As HIV-infected patients lived longer, mortality related to the progression of HCV-related advanced liver disease and its complications of liver failure, variceal

**Table 77.6:** Testing and Treatment of HCV Infection in the Setting of HIV (American Association for Study of Liver Diseases, 2009)<sup>87</sup>

- Anti-HCV testing should be performed in all HIV-infected.
- HCV RNA testing should be performed to confirm HCV infection in HIV-infected persons who are positive for anti-HCV, as well as in those who are negative and have evidence of unexplained liver disease.
- Hepatitis C should be treated in the HIV/HCV coinfecting patient in whom the likelihood of serious liver disease and a treatment response are judged to outweigh the risk of morbidity from the adverse effects of therapy.
- Initial treatment of hepatitis C in most HIV-infected patients should be peginterferon alpha plus ribavirin for 48 weeks at doses recommended for HCV mono-infected patients.
- When possible, patients receiving zidovudine (AZT) and especially didanosine (ddI) should be switched to an equivalent antiretroviral agent before beginning therapy with ribavirin.
- HIV-infected patients with decompensated liver disease (CTP score >7) should not be treated with peginterferon alpha and ribavirin and may be candidates for liver transplantation.

hemorrhage, and hepatocellular carcinoma became major causes of mortality in HCV-HIV coinfecting patients. Although an inverse relationship has been suggested between the CD4 count and hepatic fibrosis in patients with HCV-HIV coinfections, significant fibrotic progression also can occur in coinfecting patients with relatively high CD4 cell counts.<sup>82–87</sup>

Over the years, the treatment of HCV infection has evolved and the current standard therapy includes a combination of pegylated interferon and ribavirin for 24–48 weeks depending on genotype (Table 77.6).<sup>87</sup> The safety, efficacy, and tolerability of pegylated interferon and ribavirin for the treatment of HCV in HCV-HIV coinfecting patients was assessed in many published studies. Overall, the rates of sustained virological response (SVR) were lower than those observed in patients with HCV infection alone, which was in part due to excessive rates of discontinuation because of adverse events and poor tolerability of the antiretroviral drugs. Rate of SVR for genotype 1 and 4 varies from 14% to 38%, and for genotype 2 and 3 it varies from 44% to 73%.<sup>87</sup> But rate of discontinuation of drugs, mostly due to drug related adverse effects, varies from 12% to 39%. However, combination of pegylated interferon and ribavirin can not be used in all stages of HCV infection, it needs to be avoided in those with decompensated cirrhosis, advanced cirrhosis with a high risk of decompensation, significant cytopenias, active infections, immune mediated diseases, and autoimmune diseases. A Child-Turncote-Pugh (CTP) score of 7 or more or model for end-stage liver disease (MELD) score of 15 or more also portend an unacceptable rate of complications.

There is well-described hepatotoxicity associated with HAART but the current evidence suggests that HAART therapy appears to be of benefit from both the HIV and liver disease point of view, and should be considered in all coinfecting patients.<sup>80–85</sup> The results from several recent studies have indicated that liver-related outcome in coinfecting patients receiving HAART are superior to those in coinfecting patients not receiving HAART.

## HEPATITIS B VIRUS AND HIV/AIDS

Coinfection with HBV and HIV-1 is common because of the shared mode of transmission. Data indicate a wide range of coinfection prevalence (7–70%) in patients who are infected with HIV.<sup>80–86,88–93</sup> Immunologic dysfunction induced by HIV is expected to modify the course of HBV infection as 20% of HIV-infected patients become chronically infected against only 5% in the general population. The ability to clear HBsAg is dependent upon the CD4+ cell count.<sup>88–100</sup> The natural history of HIV and HBV has been altered with the advent of HAART.<sup>80–86,91</sup> There is evidence to suggest that the reconstituted immune system itself can cause an initial flare of transaminase levels, as a result of the onset of a strong cytotoxic T-lymphocyte response. Lamivudine, often administered as a component of HAART for HIV, is highly inhibitory to HBV and can lead to reductions in HBV DNA and HBeAg and normalization of aminotransferase levels in HBV-infected patients.<sup>80–86,91</sup>

Lamivudine, emtricitabine, and tenofovir are highly active against both HIV and HBV. However, the rate of HBV resistance to lamivudine in HBV/HIV coinfecting patients is high, reaching 90% in 4 years. Tenofovir plus lamivudine or emtricitabine are commonly prescribed as components of HAART in HBV/HIV coinfecting patients. Tenofovir is effective against lamivudine-resistant HBV. Adefovir in the approved dose for HBV (10 mg) has negligible activity against HIV. Entecavir has also been shown to decrease serum HIV RNA levels in lamivudine-experienced as well as in lamivudine-naïve patients. Clinical studies in patients with HBV/HIV coinfection reported lower response rates to IFN- $\alpha$  treatment than those with HBV monoinfection. Responders tend to have a higher mean CD4 cell count than nonresponders.

**Table 77.7:** Recommendations for Treatment of Patients with HBV/HIV Coinfection (American Association for Study of Liver Diseases, 2009)<sup>91</sup>

### Indications of therapy

- Patients who meet criteria for chronic hepatitis B should be treated.
- Liver biopsy should be considered in patients with fluctuating or mildly elevated ALT (1–2 times of normal)

### Choice of therapy

- Patients who are not on HAART and are not anticipated to require HAART in the near future should be treated with an antiviral therapy that does not target HIV, such as pegylated interferon or adefovir.
- Patients in whom treatment for both HBV and HIV is planned should receive therapies that are effective against both viruses: lamivudine plus tenofovir or emtricitabine plus tenofovir are preferred.
- Patients who are already on effective HAART that does not include a drug active against HBV may be treated with pegylated interferon or adefovir.
- In patients with lamivudine resistance, tenofovir should be added.
- When HAART regimens are altered, drugs that are effective against HBV should not be discontinued without substituting with another drug that has activity against HBV, unless the patient has achieved HBeAg seroconversion.

Standard criteria for treatment are applicable for the treatment of HBV infection in the setting of HIV (Table 77.7).<sup>80–86,91</sup> Given that antiretroviral regimens may include drugs with activity against HBV, it is reasonable to base HBV treatment decisions on whether or not HIV treatment is ongoing or planned. In HBeAg-positive patients who are not in need of HAART, or who are already well-controlled on HAART that does not include a drug with activity against HBV, pegylated interferon may be considered as a first-line option given its limited duration, but adefovir can also be used in this setting.<sup>80–86,91</sup> It is generally recommended that candidates for interferon therapy should have CD4 cell counts >500 cells/mL. Patients who have lower CD4 cell counts or who are HBeAg-negative may be appropriate candidates for adefovir. Finally, in HBeAg-negative patients who are likely to need HIV treatment in the future, earlier initiation of HAART may be considered. For patients in whom HAART initiation is planned, it is best to use a regimen that includes drug/drugs with activity against HBV. Most experts recommend using two drugs.<sup>80–86,91</sup> Combinations can include tenofovir plus lamivudine or tenofovir plus emtricitabine. When HAART regimens are altered, drugs that are effective against HBV should not be discontinued without substituting another drug that has activity against HBV, unless the patient has achieved HBeAg seroconversion and has completed an adequate course of consolidation treatment.

The treatment of HBV in patients with AIDS is disappointing due to the immunosuppression and comorbidity. Patients have higher levels of HBV DNA, lower pretreatment transaminase levels and less hepatic inflammation, all indicators of poor response to interferon.<sup>91–103</sup> The response rate is only 8.3% at the end of 3 months. The response rate to vaccination is also disappointing with a nonresponse in 40% as compared to 2.5–5% in immunocompetent individuals. Up to 70% of IV drug abusers have hepatitis delta virus infection, which is associated with a serious outcome. These patients have highly elevated transaminases and are more prone for reactivation and development of fulminant disease.

## OTHER VIRAL INFECTIONS

CMV hepatitis is usually subclinical and characterized by mild transaminitis and mild cholestasis. It is typically associated with sparse hepatonecrosis, periportal, and perivenous infiltrate, and cells with large intranuclear and small cytoplasmic inclusions.<sup>104</sup> It can also cause mass lesions simulating neoplasia or granulomatous infiltration. Herpes simplex virus causes severe aminotransferase elevations. On histology, it shows Cowdry type A intranuclear inclusions.<sup>104</sup> HIV infects the Kupffer cells and sinusoids, which represent a potential barrier to infection of the underlying hepatocytes. Studies have shown that it can cause limited cytolysis and alteration of the phagocytic and synthetic function.



## GRANULOMATOUS INFLAMMATION

It is characterized by elevated levels of alkaline phosphatase as a result of infiltration of hepatic parenchyma and obstruction of the terminal branches regardless of the cause. The common causes include mycobacterial, fungal, and protozoal infections.<sup>105</sup>

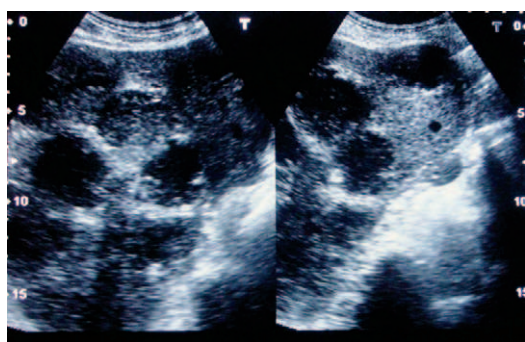
Both pyogenic and amoebic liver abscesses can complicate the course of HIV-seropositive individuals (Fig. 77.9a,b).

## FATTY LIVER (STEATOSIS) IN AIDS

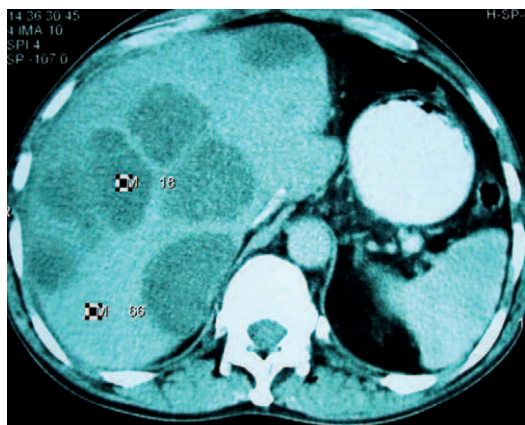
Steatosis in HIV-seropositive patients may result from HIV itself, the use of nucleoside analogs (some of which have been implicated in acute liver cell failure), and concurrent infections with hepatitis B and C.<sup>80–86,106</sup> In addition, the other common causes like alcohol and diabetes also need to be considered in this subset of individuals.

## KAPOSI SARCOMA

It is the most common hepatic neoplasm seen in patients with AIDS, usually there is associated cutaneous involvement.<sup>30–34,103–105</sup>



**Fig. 77.9a:** Ultrasound scan showing multiple pyogenic abscesses in the liver. *Courtesy: Dr. Suman Kochhar, Professor of Radiodiagnosis, GMCH, Chandigarh.*



**Fig. 77.9b:** Contrast enhanced CT scan of abdomen showing multiple abscesses in the liver. *Courtesy: Dr. Suman Kochhar, Professor of Radiodiagnosis, GMCH, Chandigarh.*

It tends to originate in the capsular, hilar, and portal areas and invades the parenchyma from these sites. Non-Hodgkin lymphoma also has a high incidence of involvement of the liver.

## HEPATOTOXIC DRUGS

Hepatotoxicity as a complication of HAART is too well-known as significant hepatotoxicity occurs in about 6% to 10% of patients.<sup>80–85,105–107</sup> The severity of the hepatotoxicities ranges from asymptomatic elevations of aminotransferase levels to fatal acute liver failure. Life-threatening events related to hepatic damage occur in about 2.6 per 100 person-years on ART. HCV infection, HBV infection, and alcohol abuse have been identified as risk factors for hepatotoxicity caused by HAART. The possible mechanisms of hepatotoxicity of HAART include direct toxicity from individual component drugs, mitochondrial toxicity of nucleoside agents, idiosyncratic hypersensitivity reactions, induction of hepatic metabolic abnormalities, and immune-mediated following reconstitution of immune activity in patients coinfecting with HIV and HCV or HBV.<sup>82–84</sup>

Nucleoside reverse transcriptase inhibitors (NRTIs) are known to have a potential for mitochondrial toxicity.<sup>82–84</sup> Pharmacologically designed to be incorporated into viral nucleic acids and to act as chain terminators, these drugs also inhibit human mitochondrial DNA polymerase  $\gamma$  (an enzyme necessary for mitochondrial DNA replication), leading to reduced mitochondrial DNA content and altered mitochondrial morphology. Toxicity typically occurs more than 6 months after initiation of therapy and manifests with lactate acidosis and elevations in serum lactic dehydrogenase, amylase, or lipase levels, as well as liver chemistry tests. In contrast, the non-nucleoside reverse transcriptase inhibitors tend to cause immune-mediated adverse drug reactions, with nevirapine-based regimens being the most frequently involved. Most reactions occur during the initial 4 weeks of therapy. In addition to elevated liver chemistry tests, clinical features of hypersensitivity such as leukocytosis, elevated immunoglobulin-E levels, and eosinophilia are typically present.

Significant hepatotoxicity is seen in about 10% of patients treated with protease inhibitors class of drugs, with ritonavir having the highest risk.<sup>82–84</sup> The incidence of toxicity tends to increase over time with duration of drug exposure. Ribavirin has significant drug interaction with many agents which are part of HAART. Ribavirin should never be used in combination with didanosine as this combination is known to lead to potentially fatal mitochondrial toxicity with lactic acidosis. Zidovudine and ribavirin should also be avoided as this combination is known to be associated with substantially greater anemia or neutropenia than observed with either agent alone.

## Patterns of Hepatotoxicity in HIV-Infected Patients on Drug Therapy (Table 77.8)

### Hepatitis and Increased Transaminase Levels

Hepatic injury is often defined as increases in aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels

**Table 77.8:** Commonly Used Hepatotoxic Drugs in HIV-Infected Patients

Hepatocellular	Cholestatic	Mixed
Zidovudine	Albendazole	Co-trimoxazole
Dideoxyinosine	Macrolides	Carbamazepine
Ketoconazole		Ganciclovir
Antitubercular drugs		
Antiepileptics		
Ganciclovir		
Pentamidine		
Nevirapine		

that are 3–5 times more than the upper limits of normal or the patient's baseline values before initiation of ART.<sup>82–84</sup> About 5–10% of patients have increased liver enzyme levels after the initiation of ART. All drug classes of ART have the potential to cause severe liver injury progressing to fulminant hepatic failure. Although the injury may be caused by ART, the differential diagnosis of such increases is vast, including acute or chronic viral hepatitis (hepatitis A, B, C or D, cytomegalovirus, Epstein–Barr virus), ethanol or substance abuse, systemic or opportunistic infections, nonalcoholic steatosis, and malignancies. Patients infected with HIV with clinical signs of hepatitis, such as fatigue, nausea, vomiting, and right upper quadrant abdominal pain and tenderness need further evaluation, and consideration must be given to stopping one or more of the drugs from the ART drug regimen. Patients with asymptomatic rise of transaminases may possibly be observed closely and followed up.

#### **Isolated Rise in Bilirubin without Raised Transaminases**

About 40% of individuals receiving atazanavir develop a significant increase in their total bilirubin level, 5% of patients develop jaundice, although none of them develop clinically significant hepatotoxicity.<sup>82–84</sup> This increase in total bilirubin level may be caused by a similar mechanism as Gilbert syndrome involving inhibition of UGT1A1 (UDP glucuronosyltransferase), an enzyme required for conjugation of bilirubin. Indinavir causes unconjugated hyperbilirubinemia in 10% of the patients; isolated rise in serum bilirubin may not require discontinuation of the drug.

#### **Hypersensitivity Syndrome**

Hypersensitivity syndrome is a life-threatening syndrome that is caused by an immune reaction to either the parent drug or a metabolite and is best described with abacavir.<sup>82–84</sup> The immune-mediated response can affect the liver as well as other organs, such as the skin, lungs, kidney, and heart. It most often occurs within the first few days of initiating therapy, but may occur as late as 8 weeks. The most common symptoms are fever, rash, nausea, and vomiting. 80% of patients have fever, and 70% have rash.

Patients may also exhibit myalgias, headache, diarrhea, pruritus, lymphadenopathy, mucocutaneous involvement, hypotension, and respiratory symptoms such as cough, dyspnea, or pharyngitis. In addition to raised transaminases, the patients can have leukopenia, thrombocytopenia, and raised creatinine levels. It is critical to have a high suspicion for the presence of this syndrome, as it may progress rapidly to multisystem organ failure. Early stoppage of the offending drug is the mainstay of the treatment and the clinical improvement may start within days of discontinuation of the offending drug.

#### **Hepatic Steatosis**

Mitochondrial damage is believed to be a prominent cause of hepatic steatosis. The NRTIs can reduce the replication of mitochondrial DNA (mtDNA) in a manner similar to their effects on the HIV DNA replication. Hepatic steatosis remains mostly asymptomatic but may be associated with symptoms suggestive of hepatitis in some patients.<sup>82–84,105,106</sup>

#### **Lactic Acidosis**

One of the most severe complications recognized as a risk of ART is the development of symptomatic hyperlactatemia with metabolic acidosis. The mitochondrial toxicity responsible for causing hepatic steatosis may also cause this disorder, which seems to be exclusive to NRTIs.<sup>82–84</sup> Disruption of oxidative phosphorylation prevents aerobic energy production and reduces lactate clearance. A patient is considered to have lactic acidosis if his pH is less than 7.3 and bicarbonate less than 20 mEq/L with any abnormal increase in serum lactate level. Lactic acidosis may develop within months to years after the initiation of ART (specifically an NRTI). Factors that increase the risk for this adverse event include NRTI use for greater than 6 months, pregnancy, female sex, age greater than 40 years, lower CD4 count, concurrent use of stavudine and didanosine, use of hydroxyurea or ribavirin with didanosine, obesity, and an increased body mass index. Patients with lactic acidosis mostly present with nonspecific signs and symptoms but severe cases may be associated with severe hepatocellular dysfunction, encephalopathy, ascites, cardiovascular instability, and multi-organ dysfunction. Patients with moderate to severe increases in serum lactate level, with an acidosis, or who are symptomatic should have their NRTI discontinued immediately. In severe cases, sodium bicarbonate therapy and hemodialysis with bicarbonate buffer have been used. Because of the proposed mechanism of mitochondrial dysfunction, several cofactors have also been used with varying success, including thiamine, riboflavin, L-carnitine, and coenzyme Q.

These represent one of the most common causes of abnormal liver enzymes, with almost 90% being treated with a hepatotoxic medication necessitating dosage reduction. Widespread use of co-trimoxazole for prophylaxis makes it the most common cause of drug-related hepatotoxicity in HIV/AIDS.

## Gallbladder and Biliary Tract Diseases

Signs of biliary tract disease in HIV-infected patients (pain, fever, and jaundice) do not differ from noninfected patients except that jaundice is less common. Besides AIDS related cholangitis, HIV-infected patients may develop biliary disease unrelated to HIV, the clinical pattern being similar regardless of the organism involved. Clinical features include right upper abdominal pain (90%), significant weight loss (75%), diarrhea (66%), jaundice (10%), and uncommonly pruritus.<sup>108–119</sup>

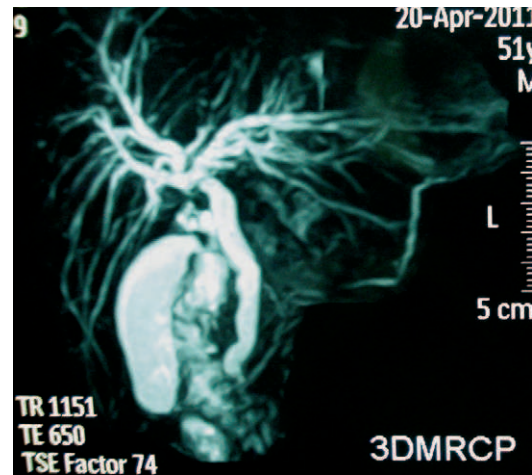
Most patients develop cholangitis years after the initial diagnosis of HIV in advanced disease.<sup>108–112</sup> AIDS cholangitis can be an AIDS defining diagnosis. Anicteric cholangitis is a predominant finding with mean alkaline phosphatase level of 750 U/dL. Serum bilirubin exceeding 2 mg/dL occurs in only 15% patients and transaminase elevation is less than twice the normal. CD4+ count is always less than 100 cells/ $\mu$ L. The pathogenesis is not known, one theory suggests a stereotypic type of injury regardless of the nature of underlying disease. Often the causes include immunologic attack, enteric infection, and ischemic injury. The organisms identified are cryptosporidium in 20–62% patients, cytomegalovirus in 23–42%, both the organisms in 23%, and microsporidia (enterocytozoon), *Mycobacterium avium intracellulare*, and *Giardia lamblia* in less than 10%.<sup>111–119</sup>

The diagnosis is based on the typical cholangiographic findings in patients with advanced HIV disease, supported by demonstration of the pathogen in the blood, stool, bile, or biopsy specimen. The organisms can be detected in up to 75% of cases.<sup>108–112</sup> Imaging modalities are the next line of investigations. Abdominal ultrasound is abnormal in 75% of cases with dilatation of common bile duct (CBD) in 65–70% and intrahepatic bile duct in 15–20% only. Overall, 20–40% have thickening of the wall of CBD and more than 50% patients have thickening of gallbladder wall, but cholelithiasis is rarely seen.<sup>111–119</sup> Computerized tomography (CT) may demonstrate intrahepatic ductal dilatation better than ultrasound.

Endoscopic retrograde cholangiopancreatography (ERCP) is the gold standard for diagnosing AIDS-related cholangitis with four distinct patterns observed.<sup>116–118</sup>

1. Papillary stenosis is seen in 15–20% of the patients with dilatation of CBD more than 8 mm and smooth distal tapering with contrast retained for over 30 minutes (Fig. 77.10).
2. Sclerosing cholangitis, characterized by focal stricture and dilatation of intra- and extrahepatic ducts, is seen in 20% of patients.
3. Combined papillary stenosis and sclerosing cholangitis is seen in 50% of the patients.
4. Long extrahepatic bile duct stricture is seen in 15% of the patients without the presence of intrahepatic strictures suggesting that another cause is present.

The common bile duct often has a beaded or scalloped appearance. The left intrahepatic biliary ductal system is often more severely affected than the right. Intraluminal polypoidal filling defects within the CBD and large intrahepatic duct occur in up to 25% of



**Fig. 77.10:** Magnetic resonance cholangiopancreatography (MRCP) showing irregular and dilated common bile duct with a stricture at lower end, classical of papillary stenosis.

cases.<sup>116–118</sup> In primary sclerosing cholangitis, the common bile duct is rarely dilated with string-like strictures and saccular deformity on cholangiogram and paucity of bile ductules on liver histology.

### THERAPY

Only a few patients will die directly from AIDS-related cholangitis. Therefore, palliation of pain should be the major goal. The response to medication is poor, though ursodeoxycholic acid reportedly improves cholestasis. As more than 70% of patients have papillary stenosis, sphincterotomy has been tried. This may result into the improvement of pain and decrease in CBD diameter, but more than one half of the patients continue to progress into intrahepatic disease. The prognosis of the condition is poor as AIDS cholangitis is a manifestation of late disease with a median survival of 7 months.<sup>112–118</sup>

### CHOLECYSTITIS

In AIDS, pain of cholecystitis is the most prominent feature, which is chronic and lasting for several months. In 66%, fever is prominent, in 50% weight loss, and in 25% vomiting is seen.<sup>118,119</sup> Laboratory data reveals a cholestatic picture. Transaminase and bilirubin levels are only mildly elevated and leukocytosis is not seen. It is a potentially serious condition requiring prompt recognition and gallbladder decompression.

Infection with cytomegalovirus, *Cryptosporidium* or both is common; rarely, *Cyclospora cayentanensis* is implicated.<sup>118–127</sup> The gallbladder wall is markedly edematous with thickness more than 1 cm. Stones are almost never found and bacterial superinfection is unusual. Patients generally have concomitant biliary disease.<sup>109</sup> Pain improves promptly following cholecystectomy. Mean survival is 7 months as acalculous cholecystitis is a late manifestation of the disease.

The presence of coexisting AIDS cholangiopathy in about half of the patients increases the likelihood of ongoing symptoms of



cholecystitis. Patients should be counseled that postoperative endoscopic retrograde cholangiopancreatography may be necessary and that some variants of AIDS cholangiopathy do not respond to endoscopic therapy.

## Pancreatic Disorders

Patients with HIV/AIDS are subject to the same diseases affecting the general population including alcoholic pancreatitis. In addition, certain other disorders peculiar to AIDS like opportunistic infections, neoplasms, and drug related side effects may occur.<sup>128–132</sup> Autopsy studies have found pancreatic lesions in 10% of patients with AIDS. Pancreatic lesions infrequently produce symptoms and are rarely recognized antemortem. Various causes and evaluation strategies for pancreatic dysfunction in AIDS are given in Table 77.9.

### ACUTE PANCREATITIS

Pancreatitis occurs in about 5% of adult patients and 17% of children with AIDS.<sup>128–137</sup> Clinical findings of pancreatitis are similar as seen in HIV-negative patients except that they are more likely to have pyrexia, diarrhea, hepatomegaly, leukopenia,

anemia, and hypoalbuminemia due to the immunosuppression and malnutrition. Unusual features of pancreatitis in AIDS include high frequency of drug induced pancreatitis (in almost 50% patients; most common offending drugs are pentamidine, dideoxyinosine, and co-trimoxazole) and low frequency of gallstone pancreatitis.<sup>128–130</sup> A significant proportion of patients with asymptomatic HIV infection have abnormally elevated serum trypsin and elastase levels, possibly only due to HIV infection. Development of pancreatitis is a poor prognostic sign in pediatric HIV patients. APACHE II scores are reasonably more sensitive and moderately robust predictors of severe disease than Ranson or modified Glasgow scale.

Although advanced HIV disease alone is associated with an increased incidence of pancreatitis, but NRTI use is independently linked to this complication. The incidence of pancreatitis in patients on didanosine (NRTI) ranges from 1% to 7%, with a 6% mortality.<sup>128–132</sup> This complication occurs most often 2–5 months after the initiation of ART. The concurrent use of didanosine with hydroxyurea increases the risk of acute pancreatitis by 4-fold. Other known risk factors are a CD4 count less than 200 cells/ $\mu$ L, age greater than 37 years, increased baseline amylase, and female gender.

The mechanism of pancreatic toxicity may be related to the mitochondrial toxicity of NRTIs. Protease inhibitors often induce hyperlipidemia, a known cause of acute pancreatitis. Approximately 50% of patients after 1 year on ART have newly diagnosed hyperlipidemia. There are several mechanisms believed to cause the dyslipidemia associated with ART, each mediated by alterations in different receptors and enzymes.

### AIDS CHOLANGIOPATHY

Pancreatogram in patients with papillary stenosis show that 81% have associated pancreatic duct dilatation, often with associated features of chronic pancreatitis.<sup>115–117</sup> It presents with a picture similar to that of sclerosing cholangitis. ERCP is the investigation of choice, which reveals localized stenosis, diverticula, saccular dilatation, and pruning of the intrahepatic ducts. It can also involve the juxta-ampullary region of the pancreas. Organisms implicated are CMV and cryptosporidia.<sup>115–117,136,137</sup>

### CHRONIC PANCREATITIS

The incidence of chronic pancreatitis in HIV-positive patients is 0.5%; the most common cause is alcohol.<sup>128–137</sup> Glucose intolerance is more likely to be due to drug toxicity, pentamidine, and dideoxyinosine being implicated. HIV itself has been known to cause beta cell dysfunction leading to type 1 diabetes.

### PANCREATIC ABSCESS

These patients are present with chronic fever, night sweats, rigors, malaise, and weight loss. Leukocytosis is not seen. Opportunistic infection with mycobacteria is among the common causes of pancreatic abscess. Kaposi sarcoma of the pancreas can mimic

**Table 77.9:** Evaluation and Differential Diagnosis of Pancreatic Dysfunction in HIV-infected Patients

<b>Hyperamylasemia without pancreatitis</b>
Due to renal failure—Heroin/AIDS nephropathy
Macroamylasemia—nonspecific B cell stimulation and polyclonal gammopathy
Salivary hyperamylasemia
<b>Acute Pancreatitis</b>
<b>AIDS-associated infection</b>
Cytomegalovirus
<i>Toxoplasma gondii</i>
<i>Cryptococcus neoformans</i>
<i>Candida albicans</i>
<i>Mycobacterium tuberculosis</i>
<i>Mycobacterium avium intracellulare</i>
<i>Cryptosporidium</i>
<b>AIDS-associated neoplasia</b> —Kaposi sarcoma and lymphoma
<b>Medications</b>
Pentamidine
Dideoxyinosine
Dideoxycytidine
Co-trimoxazole
<b>Directly caused by HIV (?)</b>
<b>Unrelated to AIDS</b> —alcohol, gallstones, trauma, hyperlipidemia
<b>Chronic pancreatitis</b>
<b>Pancreatic mass</b> —Lymphoma and Kaposi sarcoma
<b>Pancreatic abscess</b>
<i>M. tuberculosis</i>
<i>M. avium</i> complex
<i>Aspergillus</i>
<i>P. jiroveci</i>
<b>Pancreatic infection without pancreatic dysfunction</b>
Cytomegalovirus
<i>C. neoformans</i>
<i>M. avium intracellulare</i>

pancreatic cancer in HIV-infected patients. The diagnosis is made by demonstration of human herpes virus 8 (HHV-8) in the aspirated pancreatic juice/bile. There is good response to paclitaxel and antiretroviral therapy.<sup>138,139</sup>

### Non-AIDS-Related Pancreatic Disease

Alcoholic pancreatitis is more common among IV drug abusers who are more likely to have a worse prognosis, as they are severely malnourished and suffer from concomitant diseases. Gallstone pancreatitis is distinctly uncommon. Pancreatic adenocarcinoma is highly unusual but when it occurs it is more aggressive.

### Anorectal Disease (Table 77.10)

A highly risky form of unprotected anal intercourse 'bare backing' has emerged in male homosexuals posing new challenges in HIV prevention. The frequency of anorectal disease among homosexual AIDS patients is quite high.<sup>140–146</sup> Common findings in HIV-infected individuals include perirectal abscess, anal fistula, nonspecific ulcerations, and infectious proctitis; however, lymphoma and ulcerations caused by cytomegalovirus, tuberculosis, and histoplasmosis are also seen.<sup>140–143</sup> Gay bowel syndrome is characteristically seen in homosexuals practicing anoreceptive intercourse. Rectal use of nonoxynol-9 among men who have sex with men may increase the risk of transmission of HIV. There is a strong epidemiological correlation between sexually transmitted disease, anorectal disease, and HIV. The common STDs include gonorrhea, chlamydial infection, syphilis, herpes simplex, and human papillomavirus infections.<sup>141–143</sup> Idiopathic

AIDS-related ulcerations have also been described. They typically occur when the CD4 count falls below 200 cells/ $\mu$ L. They are wide mouthed erosions and occur more proximally than benign fistulas, transgressing normal sphincter planes. High-grade dysplasia is more common in patients with HIV and HPV coinfection, and also, there is a higher relapse rate and progression to anal cancer. HIV-positive patients with high HIV loads and/or history of anal dysplasia should be examined by anoscopy and biopsy from condylomata should be sent for histological examination. Anal cancer may be preceded by anal squamous intraepithelial lesions (SILs). Anal SILs were diagnosed in 36% HIV-positive patients and 7% controls in one study.<sup>146,147</sup>

### Miscellaneous

#### HIV AND ABDOMINAL TUBERCULOSIS

Abdominal tuberculosis in HIV-positive patients is a real challenge to the diagnostic acumen and therapeutic skill of a physician. Diagnosis is difficult as symptoms and signs are nonspecific.<sup>148–152</sup> Fever, weight loss, and generalized lymphadenopathy are more common in HIV-positive patients with abdominal tuberculosis, as compared with ascites and jaundice in HIV-negative patients. Tuberculosis should be considered in all HIV-infected patients presenting with diffuse abdominal lymphadenopathy with or without unexplained exudative ascites.<sup>148–152</sup> Some of them may have peripheral lymphadenopathy, especially cervical (Figs. 77.11a, b). Though small bowel involvement is common (77.12a, b, c), involvement of solid organs is more frequently reported. Hepatic, splenic, and pancreatic abscess of tuberculous etiology is more frequently found in patients with advanced HIV disease with low CD4 cell counts.<sup>148–152</sup> Other findings include anemia, intestinal obstruction, psoas abscess, and anorectal involvement.

**Table 77.10:** Causes of Anorectal Disease in HIV-infected Patients

Infections	Neoplasms
<b>Bacteria</b>	Lymphoma
<i>Chlamydia trachomatis</i>	Kaposi sarcoma
<i>Chlamydia trachomatis</i> (L 1-3 strain)	Squamous cell carcinoma
<i>Neisseria gonorrhoeae</i>	Cloacogenic carcinoma
<i>Shigella flexneri</i>	Condylomata acuminata
<i>Mycobacterium tuberculosis</i>	
<b>Protozoa</b>	<b>Others</b>
<i>Entamoeba histolytica</i>	Idiopathic ulcers
<i>Leishmania donovani</i>	Perirectal abscess/fistula
<b>Viruses</b>	
Herpes simplex	
Cytomegalovirus	
<b>Fungi</b>	
<i>Candida albicans</i>	
<i>Histoplasma capsulatum</i>	



**Fig. 77.11a:** Photograph of a patient showing right cervical lymphadenopathy in a patient with disseminated tuberculosis. Courtesy: Dr. Suman Kochhar, Professor of Radiodiagnosis, GMCH, Chandigarh.



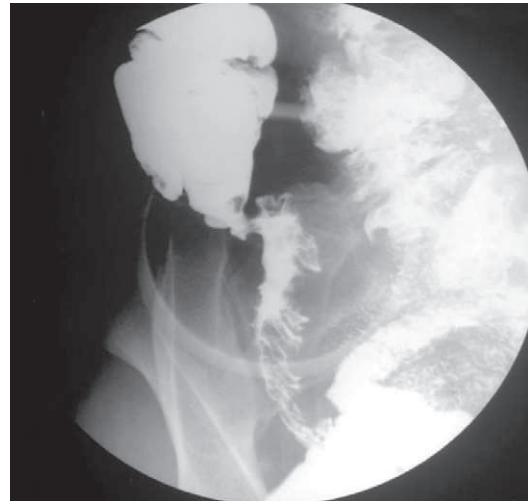
**Fig. 77.11b:** Contrast enhanced CT scan of neck of the same patient showing conglomerate mass of enlarged right cervical lymph nodes with necrosis within them. *Courtesy:* Dr. Suman Kochhar, Professor of Radiodiagnosis, GMCH, Chandigarh.



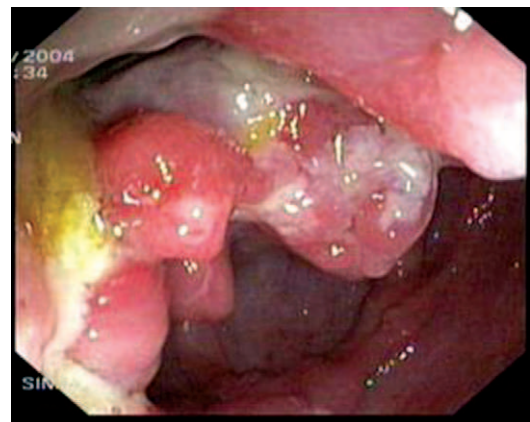
**Fig. 77.12a:** Barium meal follow through study showing features of ileo-caecal tuberculosis. *Courtesy:* Dr. B Nagi, Professor of GI Radiology, PGIMER, Chandigarh.

### HIV-ASSOCIATED NON-HODGKIN LYMPHOMA (NHL)

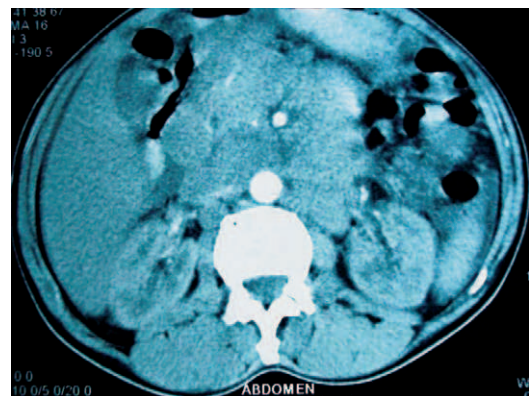
The gastrointestinal tract is a common site of involvement in HIV-associated NHL. The risk factors for this are the same as for HIV-associated extraintestinal NHL. The most common presentations include abdominal pain (77%), weight loss (77%), and gastrointestinal bleeding (38%).<sup>153,154</sup> Computed tomography in patients with NHL typically shows retroperitoneal lymphadenopathy with or without bowel involvement (Fig. 77.13). Life-threatening complications like gastrointestinal bleeding, perforation, and obstruction



**Fig. 77.12b:** Coronal image of CT scan of abdomen showing changes of ileo-caecal tuberculosis. *Courtesy:* Dr. N Kalra, Additional Professor of Radiodiagnosis, PGIMER, Chandigarh.



**Fig. 77.12c:** Colonoscopic view of ulceration and deformity of ileo-caecal area due to tuberculosis.



**Fig. 77.13:** Contrast enhanced CT scan of abdomen showing enlarged retroperitoneal lymph nodes due to lymphoma. *Courtesy:* Dr. Suman Kochhar, Professor of Radiodiagnosis, GMCH, Chandigarh.



occur in 37.5% patients with gastrointestinal tract NHL. The most common sites of involvement include large bowel (46%), ileum (39%), and stomach (23%). Those with HIV-associated gastrointestinal NHL, survive longer and are more likely to respond to therapy than those with extraintestinal HIV-associated NHL. The prognosis of AIDS patients presenting with malignant gastrointestinal lymphoma depends mainly on the presence or absence of previous AIDS defining diseases, but not CD4 counts, lymphoma-associated gastrointestinal complications or histopathological type at the time of diagnosis.<sup>153,154</sup>

### KAPOSI SARCOMA

Kaposi sarcoma is perhaps the most widely associated cutaneous manifestation of AIDS and is the most common malignancy in HIV-infected individuals.<sup>155,156</sup> Approximately 35–40% of HIV-infected patients will develop Kaposi sarcoma, and 40–67% of these lesions will occur in the head and neck region. Kaposi sarcoma lesions are large, red to violet macules. Cutaneous Kaposi sarcoma is usually asymptomatic and is primarily a cosmetic concern. Lesions can become painful if they ulcerate or become secondarily infected. Kaposi sarcoma may also present on mucosal surfaces and in lymph nodes. Epidemiological evidence suggests that KSHV/HHV-8, the causative virus, may be transmitted by faeco-oral route and HHV-8 DNA is detected in rectal samples.<sup>155,156</sup> Treatment is with liposomal anthracyclines, paclitaxel, vinca alkaloids, and cytotoxic agents.

### BACILLARY ANGIOMATOSIS

This vascular cutaneous lesion caused by *Bartonella henselae* is often accompanied by lymphadenopathy, frequently affecting the cervical lymph nodes. Other signs and symptoms include fever, anemia, lung nodules, pleural effusions, ascites, bacteremia, endocarditis, encephalopathy, and involvement of the muscle, bone, liver, or spleen.<sup>30–36</sup> Bacillary angiomatosis is most often found in the later stages of HIV disease when the CD4 count has dropped to below 200/ $\mu$ L. Lymph node and cutaneous lesions have a typical radiological characteristic in which the contrast dramatically enhances the vascular lesions and is followed by a rapid washout. The infection and lesions usually respond to erythromycin, doxycycline, or clarithromycin.

### Summary

Gastrointestinal and hepatobiliary symptoms are among the most frequent complaints in patients with human immunodeficiency virus (HIV) infection and AIDS; whole gastrointestinal tract may be involved. A wide spectrum of illnesses, some caused by HIV itself but more often caused by opportunistic infections and neoplasms are seen in these patients—those with a CD4 count <200 cells/ $\mu$ L are at the greatest risk. *Mycobacterium avium* complex is very uncommon till the CD4 count falls below 50, whereas the risk of candidiasis rises exponentially with fall in CD4 cells <100 cells/ $\mu$ L. Cytomegalovirus is the most common viral infection accounting for 45% of all esophageal ulcers on endoscopy. Diarrhea is a common manifestation occurring in about 50% of the HIV-infected individuals in developed countries and in as high as 80% in developing and underdeveloped countries. A definite cause for diarrhea can be identified in 50–80% of patients with AIDS. Patients with severe immunodeficiency (CD4, count <100 cells/ $\mu$ L) are those most at risk for Cryptosporidium, Microsporidium and CMV disease. Analysis of duodenal/bile juice is a simple, rapid, and effective method. Liver disease in patients with HIV and AIDS presents with varied symptoms including fever, right upper quadrant pain, and hepatomegaly. Almost 90% of patients have abnormalities of the liver enzymes at presentation. HCV, HIV, and hepatitis B virus (HBV) share similar routes of transmission, which include exposure to infected blood or blood products, sexual transmission among heterosexuals and MSM, and vertical transmission from infected mother to her neonate during childbirth. HIV-induced immunosuppression leads to higher HCV RNA levels and accelerated progression to chronic HCV infection. AIDS cholangitis can be an AIDS defining diagnosis. Most patients develop cholangitis years after the initial diagnosis of HIV. Abdominal tuberculosis in HIV positive patients is a real challenge to physicians, as diagnosis is difficult. Such patients have atypical disease more often with increased prevalence of non-intestinal lesions, especially lymphadenopathy and peritoneal disease. Management of all these diseases is many times difficult and expensive; non-availability of specific drugs in the developing countries can be a limitation.

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# 78

## Renal Manifestations of HIV Infection and AIDS

Frank Post • Rushi Deshpande

### Introduction

It has been more than two and half decades that we know of HIV-related renal disease. The earliest reported was HIV-associated nephropathy (HIVAN) presenting as heavy proteinuria and progressing to end stage renal disease (ESRD) in immunocompromised black persons.<sup>1</sup> Initially the progression of disease to ESRD was so rapid that HIVAN became the third most common cause of ESRD in black population aged between 20 and 64 years.<sup>2</sup> Due to prolonged survival of patients, additional comorbid conditions like diabetes and hypertension accompanied with nephrotoxic effects of highly active antiretroviral therapy (HAART), the spectrum of renal involvement has widened in HIV disease.

The prevalence of renal involvement in HIV-infected individuals varies widely in different populations around the world. The highest incidence was reported in the African-American and Black populations of Africa, so much that HIVAN became the commonest cause of ESRD in these populations. The prevalence amongst other ethnic groups, especially amongst the Caucasians has remained low. Recent data suggest a role of genetic background in the propensity to develop kidney disease. Certain variations in MYH9 and APOL1 genes make the African population uniquely susceptible to kidney disease.<sup>3</sup> Finally, availability of effective HAART has also led to a decline in individuals who develop kidney disease. Despite the large number of HIV-infected individuals in India, HIVAN has been reported only rarely.<sup>4</sup> Most biopsy studies have shown the presence of conditions other than the classically described HIVAN (see below) amongst HIV-infected individuals with kidney disease.

HIV-related renal disease presents as both acute and chronic renal failure involving the glomerulus, the tubular-interstitium, and the vessels. The treatment options include HAART, ACE inhibitors, steroids, and in case of ESRD, renal replacement in the form of intermittent hemodialysis, peritoneal dialysis, and renal transplant in selected patients. With the advent of HAART the progression to ESRD slowed, risk reduced by 40–60% and survival

on dialysis increased from 25% to 75%.<sup>5</sup> Renal diseases in HIV-infected patients still pose a significant morbidity and mortality in spite of adequate treatment. Although renal dysfunction can occur in an HIV-infected patient from a variety of incidental causes, the characteristic lesion that has been associated with HIV is the collapsing form of focal glomerulosclerosis (Table 78.1).

Some of the more common conditions seen during the course of HIV disease are described.

**Table 78.1:** Incidental Renal Disorders in HIV Infection

<b>Acute renal failure</b>
Acute tubular necrosis from hypovolemia, hypoxia, and toxic injuries. Allergic interstitial nephritis as a result of drugs. Severe hypoalbuminemia as a result of massive proteinuria Post-infection immune complex glomerulonephritis Crystal-induced renal failure (sulfadiazine, acyclovir, indinavir, etc.) Plasmacytic interstitial nephritis Hemolytic uremic syndrome and thrombotic thrombocytopenic purpura
<b>Chronic HIV nephropathies</b>
HIV-associated nephropathy (HIVAN) HIV immune complex kidney disease (HIVICK) Thrombotic microangiopathy
<b>Fluid, electrolyte, and acid–base derangements</b>
Hyponatremia Inappropriate secretion of antidiuretic hormone Hypokalemia and hyperkalemia Type IV renal tubular cell acidosis Hypomagnesemia
<b>Infections in the kidney</b>
Renal microabscesses from bacterial infections Tuberculosis Cytomegalovirus lesions Cryptococcus, Aspergillus, and other fungal diseases
<b>Infiltrative diseases of the kidney</b>
Lymphoma Kaposi sarcoma Amyloidosis Calcification



## Acute Renal Failure

The HAART era has seen the maximum rise in acute renal failure (ARF) in HIV patients. The incidence is about 20% in hospitalized patients with a consequent increase in hospital mortality.<sup>6</sup> Commonest etiology cited is drug induced, commonly used drugs like indinavir, tenofovir, and atazanavir require dose adjustment. Hemolytic uremic syndrome and HIVAN remain important causes of ARF in HIV patients. Others include HIV patients with liver or chronic kidney disease and opportunistic infections. In HIV patients with ARF, co-infection with HCV, underlying chronic kidney disease, old age, and more advanced disease are known risk factors with poor outcome.<sup>7</sup> Care must be taken to avoid hypotension and nephrotoxic agents and also to adjust dosage of renally excreted medications.

## Chronic HIV Nephropathies

Chronic kidney disease in HIV patients majorly includes HIVAN, HIV immune complex kidney disease (HIVICK) and thrombotic microangiopathies.

### HIV-ASSOCIATED NEPHROPATHY (HIVAN)

Following diabetes and hypertension, it is the third commonest cause of ESRD in young and middle-aged African Americans. Ratio of the diseased in the black population as compared to the white is 12:1.<sup>8</sup>

HIVAN presents with:

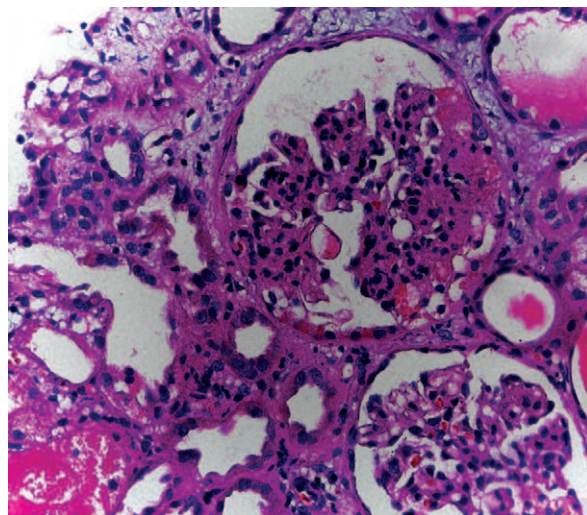
1. Nephrotic range proteinuria.
2. Edema due to hypoalbuminemia.
3. Hypercholesterolemia.
4. Hypertension—not a very common feature even in advanced disease.

Investigations show:

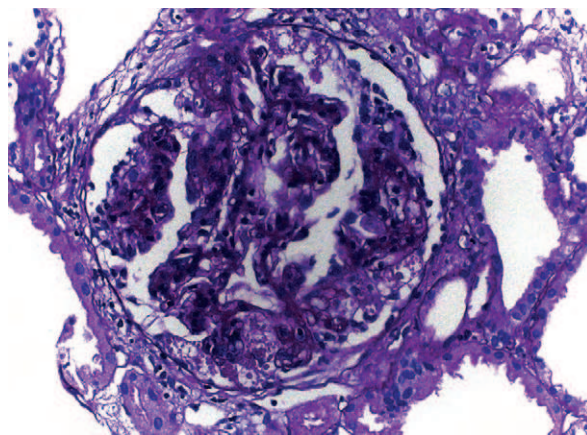
1. Presence of renal tubular epithelial cells in urinary sediment.
2. Normal or large echogenic kidneys on ultrasound.<sup>9–11</sup>
3. Microhematuria.
4. Sterile pyuria with sub-nephrotic proteinuria is also been reported in some patients.
5. Early HIVAN may present as microalbuminuria with normal glomerular filtration rate (GFR).

### Pathological Hallmark (Fig. 78.1 and 78.2):

1. Presence of focal segmental glomerulosclerosis (FSGS) on light microscopy.
2. Involves all parts of the kidney with collapse of glomerulus.
3. Podocyte proliferation, tubular atrophy with microcystic dilatation.<sup>12</sup>
4. Mononuclear cell infiltration with edema and fibrosis of interstitium.



**Fig. 78.1:** HIVAN. Light microscopy showing collapsing variant of FSGS: H&E ×400.



**Fig. 78.2:** HIVAN. Light microscopy showing collapsing variant of FSGS: PAS ×200.

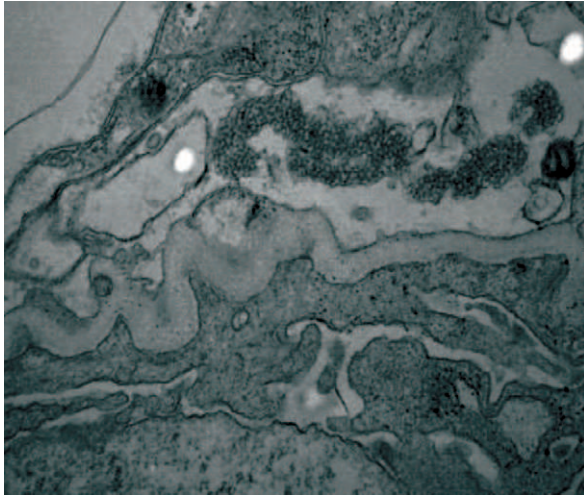
5. Mesangial hyperplasia (more common in children<sup>13,14</sup>).
6. C3 and IgM are seen on immunofluorescence.
7. EM shows retraction of glomerular basement membrane with no immune deposits and tubular reticular inclusions in endothelial cells (Fig. 78.3).

Isolation of HIV-1 from tubular epithelial cells, glomerular epithelial cells, and interstitial leukocytes has proved the direct affection of HIV-1 of the kidney.<sup>15</sup> Podocytes undergo proliferation and dedifferentiation because of expression of maturity markers including WT-1 and synaptopodin.

Patients of African heritage (black ethnicity) and those who have advanced HIV disease are at high risk.<sup>16</sup> Severity of histological damage of kidneys remains an important predictor of outcome.

Treatment mainly constitutes:

1. HAART therapy: In a study it was shown that patients initiated on early HAART did not develop HIVAN.<sup>17</sup>



**Fig. 78.3** EM showing retraction of glomerular basement membrane with no immune deposits and tubular reticular bodies in endothelial cells:  $\times 10,000$ .

In another study, suppression of HIV replication was observed in biopsy-proven HIVAN patients, who were initiated on early HAART.<sup>18</sup> FSGS may respond to corticosteroid therapy with short-term improvement in clinical parameters.

2. ACE inhibitors modulate matrix production and mesangial cell proliferation, preventing proteinuria and slow the progression to renal failure.<sup>19–21</sup>
3. Renal transplant remains a viable option in selected patients.<sup>22,23</sup>

## HIV-Associated Immune-Mediated Glomerulopathies

### IMMUNE MEDIATED

Deposition of immune complexes which contain HIV antigen and antibody to gp 120 HIV<sup>24</sup> cause HIV immune complex kidney disease (HIVICK). Deposits mainly contain IgG, C1q, and C3.

These deposits are seen in mesangial, sub-endothelial, intra- and epimembranous deposits. Histologically, these lesions are characterized by endocapillary proliferation with parietal fibrinoid deposits in multiple sites. Resemblance to lupus glomerulonephritis is seen in areas of intense deposits. As compared to HIVAN, progression to renal failure is slow and interstitial infiltrates contain increased number of “B” cells.

### IGA NEPHROPATHY

IgA nephropathy in HIV-infected patients is not uncommon. They have mild urinary abnormalities and less involvement of the glomerulus, with some mesangial deposits and mesangial hypertrophy.<sup>25</sup> In these patients, immune complexes have anti-idiotypic IgA reacting with anti gp41 IgG.<sup>26</sup>

## Co-infections

Patient with HCV and HIV co-infection have poor outcome. There is increasing prevalence of HCV co-infection in HIV patients probably because of increasing numbers of intravenous drug abusers in the HIV positives. Patient presents with renal insufficiency, microscopic hematuria with acute urine sediment, hypertension, and nephrotic range proteinuria without hypercholesterolemia. Decreased complement levels and cryoglobulinemia were seen in one third of the patients. Patients rapidly progress to renal failure requiring dialysis.

The commonest renal biopsy finding is of membranoproliferative glomerulonephritis (MPGN) and less frequently membranous glomerulopathy. Hypocomplementemia, cryoglobulinemia, hypertension, and microscopic hematuria differentiate HCV-associated glomerulonephritis (GN) in HIV patient from HIVAN but renal biopsy is essential.<sup>27</sup>

Renal amyloidosis<sup>28</sup> and fibrillary immunotactoid GN<sup>29</sup> are infrequently observed in a HIV-infected patient.

## HIV-Associated Thrombotic Microangiopathy

Boccia et al.<sup>30</sup> first described thrombotic microangiopathies involving the kidney in HIV-positive patients. The prevalence is variably reported worldwide.

Microangiopathic hemolytic anemia with renal insufficiency, thrombocytopenia, fever, and neurological changes are commonly seen, though thrombocytopenia is predominant in thrombotic thrombocytopenic purpura (TTP), microangiopathic hemolytic anemia and renal failure predominates in hemolytic uremic syndrome (HUS). They are more common in young (mean age 35 years) with male (80%) predominance. Absence of massive proteinuria differentiates it from HIVAN and immune-mediated diseases.<sup>31</sup>

Pathogenesis involves direct endothelial damage, renal cellular apoptosis, and von Willebrand factor—cleaving protease inhibition. Histologically, it shows platelet fibrin thrombi in glomerular capillaries, renal arterioles, and inter-lobular arteries, endothelial cell edema, arterial intimal edema, fibrinoid necrosis, mesangiolysis, and onion skin lesions. Immunofluorescence shows fibrin and fibrinogen in arterioles and the glomerular deposits of fibrinogen, C1q, C3, C4, IgA, and IgM and light chains. On electron microscopy tubuloreticular lesions are seen in endothelial cells in blood vessels.<sup>32</sup>

Treatment options include HAART with plasmapheresis and splenectomy in refractory cases. Despite aggressive treatment HIV-TTP/HUS has high mortality early in the disease.<sup>33</sup>

## Electrolyte Disorders

1. Hyponatremia is seen in 40% of the patients and is commonly due to loss through GI tract, adrenal insufficiency, and syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH) secondary to pulmonary and central nervous system infections.<sup>34</sup>



- Hyperkalemia is seen in affected patients with adrenal insufficiency, ARF and pentamidine therapy.
- Hypokalemia is seen in patients with GI losses due to diarrhea.
- Metabolic alkalosis is observed in patients with prolonged vomiting.
- Patients on pentamidine therapy have hypomagnesemia and symptomatic hypocalcemia due to renal magnesium wasting.<sup>35</sup>

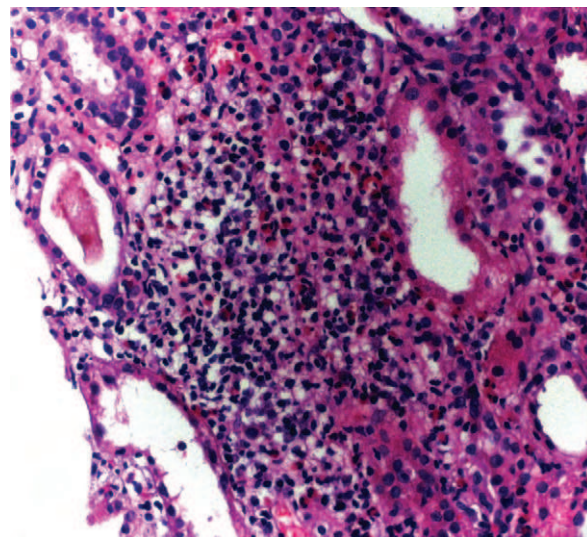
## Renal Infections

Multidrug-resistant tuberculosis is highly prevalent in HIV-positive patients.<sup>36</sup> Extra pulmonary infection like renal tuberculosis is seen frequently, which is rather difficult to diagnose and treat due to drug interactions. Opportunistic infections like histoplasmosis, aspergillosis, toxoplasmosis, cytomegalovirus (CMV) and *Pneumocystis jiroveci* may affect the kidney.<sup>37</sup>

CMV is known to cause acute tubular necrosis (ATN) and is also postulated to cause HIVAN.<sup>38</sup>

## Nephrotoxic Effects of HAART (Table 78.2)

Many antiretroviral drugs are implicated to cause renal injury; most frequently indinavir and tenofovir have been implicated. Indinavir causes nephrolithiasis and interstitial nephritis due to crystallization in the urinary tract. Progression to chronic kidney disease is not uncommon but usually it resolves with hydration and drug discontinuation.<sup>39</sup> Tenofovir is implicated in the development of ARF, progressive renal failure, renal tubular acidosis, Fanconi syndrome, nephrogenic diabetes insipidus, hypokalemia, osteomalacia, and urinary concentration defects.<sup>40</sup> Discontinuation of the drug usually resolves the renal failure. Tenofovir with didanosine and boosted PIs, old age, advanced disease, low body mass are



**Fig. 78.4:** Drug-induced interstitial nephritis showing inflammatory mononuclear cells in the interstitium H&E × 400.

risk factors for renal impairment.<sup>41</sup> Atazanavir is known to cause kidney stones, acute interstitial nephritis (Fig. 78.4) and chronic kidney disease.<sup>42</sup>

## Dose Modification of ARV in Adults with Renal Dysfunction (Table 78.3)

### Nucleoside/tide Reverse Transcriptase Inhibitors (NRTIs)

Most NRTIs, including didanosine (ddI), emtricitabine, stavudine (d4T), tenofovir (TFV), zalcitabine, and lamivudine are eliminated primarily unchanged in the urine. Zidovudine and abacavir undergo substantial hepatic biotransformation, and

**Table 78.2:** Antiretrovirals Shown to be Potentially Nephrotoxic<sup>43</sup>

Drug	Reported nephrotoxicity	Risk factor(s)
Abacavir	Acute renal failure, interstitial nephritis (rare)	...
Atazanavir	Case reports of nephrolithiasis, interstitial nephritis, reversible renal failure	Not established
Didanosine	Tubular dysfunction (rare)	...
Efavirenz	Single report of hypersensitivity reaction	...
Enfuvirtide	Single report of glomerulonephritis	...
Indinavir	Nephrolithiasis, crystalluria, dysuria, papillary necrosis, acute renal failure	Concomitant treatment with low-dose ritonavir; for nephrolithiasis, urine pH >6, low lean body mass, treatment with trimethoprim-sulfamethoxazole or acyclovir, chronic infection with hepatitis B or hepatitis C virus, warm environmental temperature, high indinavir concentration
Lamivudine	Tubular dysfunction (rare)	...
Ritonavir	Reversible renal failure, but nephrotoxicity not definitely established	Concomitant treatment with nephrotoxic drugs, underlying renal pathology
Stavudine	Tubular dysfunction (rare)	...
Tenofovir	Tubular toxicity, Fanconi syndrome (rare), decreased glomerular filtration rate	Low body weight, impaired baseline renal function, concomitant treatment with potentially nephrotoxic drugs



**Table 78.3:** Nucleoside or Nucleotide Dosage Adjustment for HIV-infected Patients with Reduced Glomerular Filtration Rate

Antiretrovirals	Daily dosage	Dosing in the case of renal insufficiency
<b>Nucleoside reverse-transcriptase inhibitor</b>		
Abacavir	300 mg PO BID	No need for dosage adjustment
Didanosine	If >60 kg, 400 mg PO QD; if <60 kg, 250 mg QD	For CrCl of 30–59 mL/min, 200 mg for weight >60 kg and 125 mg for weight <60 kg For CrCl of 10–29 mL/min, 125 mg for weight >60 kg and 100 mg for weight <60 kg For CrCl of <10 mL/min, 125 mg for weight >60 kg and 75 mg for weight <60 kg For patients undergoing CAPD or HD, use same dose as for CrCl <10 mL/min
Emtricitabine	200 mg Oral capsule PO QD or 240 mg (24 mL) oral solution PO QD	For CrCl of 30–49 mL/min, capsule of 200 mg every 48 h or solution of 120 mg every 24 h For CrCl of 15–29 mL/min, capsule of 200 mg every 72 h or solution of 80 mg every 24 h For CrCl of <15 mL/min, capsule of 200 mg every 96 h or solution of 60 mg every 24 h or HD*
Lamivudine	300 mg PO QD or 150 mg PO BID	For CrCl of 30–49 mL/min, 150 mg QD For CrCl of 15–29 mL/min, 150 mg one time, then 100 mg QD For CrCl of 5–14 mL/min, 150 mg one time, then 50 mg QD For CrCl of <5 mL/min, 50 mg one time, then 25 mg QD or HD*
Stavudine	If >60 kg, 40 mg PO BID; if <60 kg, 30 mg PO BID	For CrCl of 26–50 mL/min, 20 mg every 12 h for weight >60 kg and 15 mg every 12 h for weight <60 kg For CrCl of 10–25 mL/min, 20 mg every 24 h for weight >60 kg and 15 mg every 24 h or HD*
Tenofovir	300 mg PO QD	For CrCl of 30–49 mL/min, 300 mg every 48 h For CrCl of 10–29 mL/min, 300 mg twice weekly for ESRD, 300 mg every 7 days or HD*
Tenofovir plus emtricitabine	1 Tablet PO QD	For CrCl of 30–49 mL/min, tablet every 48 h For CrCl <30 mL/min, not recommended
Zidovudine	300 mg PO BID	For “severe” renal impairment or HD*, 100 mg TID or 300 mg QD
<b>Non-nucleoside reverse-transcriptase inhibitor</b>		
Delavirdine	400 mg PO TID	No dosage adjustment necessary
Efavirenz	600 mg PO QD, 1 tablet PO QD	No dosage adjustment necessary; Atripla not recommended if CrCl <50 mL/min
Efavirenz-tenofovir-emtricitabine	600 mg PO QD, 1 tablet PO QD	Atripla not recommended if CrCl <50 mL/min
Nevirapine	200 mg PO BID	No dosage adjustment necessary
<b>Protease inhibitor</b>		
Atazanavir	400 mg PO QD	No dosage adjustment necessary for patients not requiring HD
Darunavir	600 mg Plus 100 mg ritonavir PO BID	No dosage adjustment necessary
Fosamprenavir	1400 mg PO BID	No dosage adjustment necessary
Indinavir	800 mg PO every 8 h	No dosage adjustment necessary
Lopinavir-ritonavir	400-100 mg PO BID or 800-200 mg PO QD (QD for treatment-naïve patients only)	No dosage adjustment necessary
Nelfinavir	1250 mg PO BID	No dosage adjustment necessary
Ritonavir	600 mg PO BID	No dosage adjustment necessary
Saquinavir soft gel cap	1200 mg TID	No dosage adjustment necessary
Tipranavir	500 mg PO BID; with ritonavir 200 mg PO BID	No dosage adjustment necessary
<b>Entry inhibitor</b>		
Enfuvirtide	90 mg Subcutaneously every 12 h	No dosage adjustment necessary
Maraviroc	The recommended dose differs on the basis of concomitant medications because of drug interactions: 150 mg, 300 mg, or 600 mg BID	No dosage recommendation; use with caution; patients with CrCl <50 mL/min should receive maraviroc and CYP3A inhibitor only if potential benefit outweighs the risk
<b>Integrase inhibitor</b>		
Raltegravir	400 mg BID QD	No dosage adjustment

**Note:** Adapted from US Department of Health and Human Services guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.

Atripla, efavirenz-emtricitabine-tenofovir; BID, twice per day; CAPD, continuous ambulatory peritoneal dialysis; CrCl, creatinine clearance level; ESRD, end-stage renal disease; HD, hemodialysis; HD\*, dose after HD; PO, orally; QD, every day; TID, 3 times per day.

therefore may require less or no dose reductions. Tenofovir may be used in ESRD patients since it can be dosed once weekly, thus decreasing pill burden and reducing the annual cost.

Fixed-dose co-formulations are to be avoided in patients with significant renal dysfunction because renal excretion of all the components is not identical.

### Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Dose modifications are not required for patients with renal insufficiency as NNRTIs undergo hepatic metabolism.

### Protease Inhibitors (PIs)

Available PIs (atazanavir, darunavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir/ritonavir, saquinavir, and tipranavir) are highly metabolized in the liver. Dose adjustment is not required for patients with renal insufficiency. Indinavir is associated with nephrolithiasis due to precipitation in the urinary tract. Atazanavir has also been associated with nephrolithiasis and is the only protease inhibitor that has a specific warning against use in patients on hemodialysis as there is 40% reduced absorption relating to lower gastric pH in these patients.

### Entry Inhibitors

Maraviroc is a CCR5 inhibitor, with 25% of the drug being eliminated through the kidneys. Maraviroc should be used with caution in patients with renal dysfunction; if the creatinine clearance is less than 50 mL/min. Combination of maraviroc and ritonavir should only be used "if the potential benefit outweighs the risk." Fusion inhibitor enfuvirtide requires no dose modification in patients with renal dysfunction.

### Integrase Inhibitors

Raltegravir is metabolized via UGT1A1 glucuronidation, hence is a safe drug requiring no dosing adjustments for patients with renal or hepatic dysfunction.

### TIMING OF DOSES FOR PATIENTS ON HEMODIALYSIS

Antiretroviral drugs that are not likely to be dialyzed are zidovudine, lamivudine, abacavir, efavirenz, etravirine, delavirdine, nelfinavir, saquinavir, indinavir, ritonavir, lopinavir, and fosamprenavir. Postdialysis dosing results in optimal serum concentrations. Drugs like didanosine, stavudine, and zalcitabine are most likely to be removed by dialysis so are best avoided or dosed post dialysis.

### Renal Transplantation in Patients with HIV Infection

HIV infection was a contraindication to transplantation in the past because of limited supply of donor organs, possibility of

exacerbation of the immunocompromised state by administration of additional immunosuppressants, unknown long-term outcome and risk of transmission to the staff members.<sup>44</sup>

Changes in the trend were seen by the advent of HAART as it has turned HIV into more of a chronic infection. Studies have shown greater than 80% graft survival at 1–3 years after kidney transplantation in patients on HAART. Rate of acute graft rejection is more compared to HIV-negative patients. Progression of liver disease is a major concern in renal transplant recipients with co-infection of HIV and HCV.<sup>45,46</sup>

### PROPOSED CRITERIA FOR RENAL TRANSPLANTATION<sup>47,48</sup>

#### Inclusion Criteria

- Meeting standard criteria for inclusion in renal transplantation list.
- CD4+ T-cell count  $\geq 200/\mu\text{L}$  at any time in the 16 weeks before transplantation.
- No change in antiretroviral regimen for 3 months before transplantation.
- Primary medical care provider has expertise in HIV treatment.
- Ability and willingness to comply with immunosuppression protocol and antiretroviral therapy.
- Ability and willingness to undergo prophylaxis for Pneumocystis pneumonia, herpes virus, and fungal infection.
- If hepatitis C co-infection is present, ability, and willingness to undergo frequent post-transplantation monitoring including hepatitis C treatment as mandated by medical care provider and collection of liver biopsy samples.
- If a history of pulmonary coccidioidomycosis exists, patient must be disease free for at least 5 years before transplantation.
- If a history of neoplasms such as cutaneous Kaposi sarcoma, *in situ* anogenital carcinoma, adequately treated basal or squamous cell carcinoma of the skin or solid tumors treated with curative therapy exists, the patient must be disease free for at least 5 years before transplantation.
- If a history of renal cell carcinoma exists, patient must be disease free for at least 2 years before transplantation.
- Ability to provide informed consent. For children under the age of 7 years, only the parent can provide consent. For children aged 7–12 years, the parental or legally responsible person must provide informed consent and the minor must sign an assent. In the case of a minor between ages 13 and 18 years, the minor and parent(s) must provide informed consent.
- Female candidates of child-bearing potential must have a negative serum human chorionic gonadotropin chain beta pregnancy test 14 days before transplantation. All candidates must practice barrier contraception.

#### Exclusion Criteria

- Age <1 year.
- Detectable HIV-1 RNA.

- History of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis of at least 1 month duration, lymphoma (Burkitt, immunoblastic, or of brain).
- History of multidrug-resistant fungal infection (e.g., resistant *Candida krusei* or *Candida glabrata* infection) not expected to respond to available oral antifungal agents.
- History of any neoplasm except those specified in the inclusion criteria.
- Substance use as per local transplantation policy.
- Advanced cardiac or pulmonary disease as per local transplantation policy.
- Anatomic abnormalities precluding transplantation.
- Use of interleukin 2 or granulocyte-macrophage colony-stimulating factor in the 6 months before transplantation.
- Cirrhosis on liver biopsy in patients with hepatitis C co-infection, unless candidate is being listed for combined liver and kidney transplant.
- Substantial wasting and/or malnutrition.
- Concomitant conditions that, in the judgment of care providers, preclude transplantation or immunosuppression.

### IMMUNOSUPPRESSIVE STRATEGIES

Initially in HIV patients, regimen of steroids, calcineurin inhibitors (CNI), and mycophenolate mofetil (MMF) were used for immunosuppressive regimens for maintenance therapy.<sup>49</sup> However organ recipients with HIV can amount to alloimmune response,<sup>50</sup> and renal transplant recipients have higher rejection rates. Hence induction therapy with interleukin 2 receptor inhibitor (to deplete CD4+ T cells) is used which successfully reverses aggressive rejection in several patients.<sup>51,52</sup>

Antiretroviral properties are seen in most of the post-transplantation maintenance immunosuppressive drugs like mycophenolate mofetil, CNI, and sirolimus.

Mechanism of action of MMF is by guanosine nucleoside depletion and imparts virostatic effect.<sup>53,54</sup> CNI interferes with HIV protein function.<sup>55</sup> Cyclosporine and tacrolimus have well-documented antiretroviral effects through selective inhibition of infected cell growth.<sup>56,57</sup> Sirolimus causes suppression of T-cell activation, suppression of antigen presenting cell function, disruption of infective virion replication and decrease of expression of C-C chemokine receptor type 5 on monocytes and lymphocytes.<sup>58</sup>

### Drug Interactions

1. NNRTIs induce CYP3A4, hence NNRTIs, like nevirapine and efavirenz, administered with CNI lead to decrease in CNI levels.<sup>59,60</sup>
2. Patients on PIs and cyclosporine require only 20% of immunosuppressant dose as compared to non-HIV renal transplant patients. The pharmacologic interactions are well documented in a study describing the pharmacokinetics and dosing modifications of cyclosporine, sirolimus, and tacrolimus in 35 liver or kidney transplant recipients on NNRTIs, PIs or both.<sup>61</sup>

3. Ritonavir boosts the plasma levels of other PIs (ritonavir inhibits p-glycoprotein & CYP3A4). In patients on tacrolimus or sirolimus dosing interval is increased fivefold and immunosuppressant dose decreased markedly. Co-administration of CNI and PIs leads to increase in levels of CNI (P-glycoprotein & CYP3A4 activity).
4. Patients on steroids are often co-administered a proton pump inhibitor which reduces intestinal absorption of PI atazanavir, hence avoid this combination,<sup>62,63</sup> or the treatment to be boosted by the administration of ritonavir.<sup>64</sup>
5. *In vitro* evidence suggests that MMF is antagonistic to the anti-HIV replication effects of zidovudine and stavudine,<sup>65</sup> so these drug combinations should probably be avoided. Zidovudine and MMF can lead to added myelosuppressive effect.
6. Extreme bradycardia was noted with lopinavir/ritonavir given to patients on metoprolol and lacidipine due to enzyme induction.<sup>66</sup>
7. Dolutegravir S/GSK1349572 represents a new unboosted integrase inhibitor currently under development, which is given once-daily. It has a low pharmacokinetic variability and predictable exposure-response relationship.<sup>67</sup>
8. Pharmacokinetic interactions are anticipated when voriconazole is administered with HIV protease inhibitors and NNRTIs because of enzyme induction causing decreasing trough levels of these drugs.<sup>68</sup>
9. Anti-HIV drug efavirenz levels are found to be high in patients on antituberculars and this is due to increased susceptibility of the CYP2B6 variant to inhibition by one or more of the anti-TB drugs or inhibition of an alternative pathway (e.g., CYP2A6).<sup>69</sup>

### Summary

Kidney disease is an important complication of HIV infection, especially in those with advanced disease. Its development is heavily influenced by the genetic background and availability of effective therapy in early stages. We must think beyond HIVAN when we discuss about HIV and renal diseases. HIV-associated kidney disease is characterized by some unique pathologic characteristics, the most recognizable of which are collapsing focal segmental glomerulosclerosis. Almost any renal syndrome including electrolyte derangements can be encountered in these individuals. There is no specific therapy and prevention using early HAART remains the best approach to prevent kidney disease. In the era of HAART therapy drug interactions and drug-induced interstitial nephritis must be kept in mind. Drug dosages should be adjusted as per creatinine clearance and nephrotoxic drugs should be avoided. Drug interactions between antiretrovirals and various other medications needed for management of kidney disease need attention. All forms of renal replacement therapy including kidney transplantation can be offered to individuals who develop ESRD. Careful and scientific approach utilizing the wide armamentarium against HIV and renal disease, one can significantly reduce morbidity and mortality in these patients.

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# HIV and Endocrine Manifestations

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Since the introduction of antiretroviral therapy, the morbidity and mortality from HIV infection has decreased. HIV infection is now a manageable infection that can be controlled with drugs. However, adrenal, gonadal, thyroid, bone, and metabolic abnormalities like diabetes mellitus and lipodystrophy are common in HIV-infected patients. These occur because of the result of HIV itself, immunologic-cytokine mediated factors, antiretroviral drugs and opportunistic infections or the interaction of these factors.

### Adrenal Dysfunction

The hypothalamic-pituitary-adrenal axis involvement is common in patients with HIV-infection. Usually the involvement is subclinical, and clinically evident adrenal insufficiency is uncommon because symptoms do not appear until more >80% of gland has been destroyed.<sup>1</sup> The extent of necrosis reported in autopsy findings of cytomegalovirus (CMV) adrenalitis, rarely exceeds 60%. Adrenocortical antibodies are detected in a substantial proportion of patients with AIDS due to nonspecific B cell activation.<sup>2</sup> Adrenal insufficiency usually occurs in the advanced stages of infection and can be primary due to direct involvement of the adrenal or secondary alteration due to involvement of hypothalamic pituitary adrenal axis.

#### CAUSES OF ADRENAL INSUFFICIENCY

##### (A) Primary

- Infections: Tuberculosis, HIV, cytomegalovirus, cryptococcus, toxoplasmosis, histoplasmosis.
- Tumor: Kaposi sarcoma, lymphoma, hemorrhage.
- Medications: Ketoconazole, fluconazole, rifampicin, etomidate.

##### (B) Secondary/tertiary

- Infection/Infiltration: Tuberculosis, sarcoidosis, hemochromatosis.
- Medications: Megestrol, exogenous steroids.
- Tumors, trauma, isolated ACTH deficiency.

On the contrary, elevated basal cortisol level and lower dehydroepiandrosterone (DHEA) levels in the absence of Cushing syndrome are common in HIV-infected patients. These are attributed to the shift from Th1 to Th2 immunologic response.<sup>3</sup> Some patients with AIDS have a syndrome of peripheral cortisol resistance due to acquired abnormalities of glucocorticoid receptor (GR), characterized by increase in GR density, decrease in GR affinity for the substrate, high serum cortisol with low ACTH, Addisonian features and increased production of IFN- $\alpha$ .<sup>4</sup> Basal aldosterone levels are usually low in HIV-infected individuals. Protease inhibitors may cause mildly elevated basal cortisol or 24-hour urine cortisol level. However, cortisol levels are suppressed normally in response to dexamethasone.

The principle metabolic route of glucocorticoids is via the cytochrome p450 3A4 enzyme. Ritonavir, a protease inhibitor (PI) used in the treatment of HIV infection, is an extremely potent inhibitor of cytochrome p450 3A4 activity. When both ritonavir and inhaled fluticasone are administered together there is an increased risk of developing Cushing syndrome with secondary adrenal suppression. These effects are not limited to ritonavir alone and can be seen with other PIs also. Fluticasone is highly lipophilic, has greater volume of distribution, and prolonged receptor occupancy. The iatrogenic Cushing syndrome may be mistaken for HIV-lipodystrophy and result in delayed diagnosis. In HIV-infected individuals with asthma, administration of both PIs and fluticasone needs to be avoided.<sup>5</sup>

### Androgen Deficiency

Hypogonadism is prevalent among HIV-infected men with low weight and wasting. In AIDS-related wasting, the prevalence of hypogonadism is about 50%. Recent reports have shown hypogonadism to be present in 20% of men on highly active antiretroviral therapy (HAART).<sup>6</sup> The usual cause of hypogonadism among men is "hypogonadotrophic hypogonadism" which is often due to multiple factors such as malnutrition, severe illness and drugs such as opiates, megestrol acetate, steroids, and anabolic steroids. Hypogonadism may also be due to a primary testicular



etiology, which can be due to infections or drugs. Among women, inadequate adrenal androgen secretion in association with severe illness may contribute to reduced overall androgen levels.<sup>7</sup>

Increased serum hormone binding globulin (SHBG) levels are seen in HIV-infected patients (30–55%). This results in relative increases in total testosterone levels that may over estimate bioavailable testosterone. Measurement of free testosterone, unbound to SHBG rather than total testosterone is advisable when hypogonadism is being evaluated in HIV-infected patients. Hyperprolactinemia has been reported in 21% of HIV-infected men with stable HIV disease and was significantly associated with opioid use and increased CD4 count but not with changes in body composition or gynecomastia.<sup>8</sup> Increased serum prolactin in association with galactorrhea has also been described among HIV-infected patients treated with PIs, both men and women.<sup>9</sup> Hypogonadism is associated with reduced muscle mass, decreased strength, and decreased functional status. Reduced androgen levels are also associated with bone loss and depression. Treatment of hypogonadal HIV-infected men has been shown to increase muscle mass, strength, and improve bone mass and depression indices.<sup>10</sup>

## Thyroid Dysfunction

Thyroid function abnormalities are common in HIV-infected patients. In HIV-infected patients, thyroxine binding globulin (TBG) levels are often elevated and correlate inversely with CD4 cell counts. Total T4 may not be reliable when assessing thyroid function due to increased protein binding. Direct measurement of freeT4 (FT4) is essential in HIV-infected individuals. Isolated low FT4 levels with concurrent normal TSH levels are found frequently among HIV-infected individuals, with a prevalence varying between 1.3% and 6.8%.<sup>11</sup> Pediatric HIV-infected patients on HAART were found to have an increased prevalence of isolated low FT4 levels (31%). Isolated low FT4 levels have been associated with didanosine, stavudine, and zidovudine. The mechanism causing low FT4 levels have not been elucidated. The clinical significance of a low FT4 level is unclear, because these patients do not have hypothyroid symptoms. Follow-up with annual thyroid function testing is advocated.<sup>12</sup>

The prevalence of hypothyroidism is increased in HIV infected individuals (0–2.6%) compared to general population (0.3%). Onset of Hashimoto thyroiditis does not appear to be common during HAART-associated immune reconstitution. Subclinical hypothyroidism is common, especially among HIV-infected patients who are receiving HAART with a prevalence of between 3.5 and 12.2%.<sup>13</sup> The prevalence of subclinical hypothyroidism is higher in men and in those with low CD4 cell count. Thyroid peroxidase (TPO)-autoantibodies are only rarely associated with subclinical hypothyroidism implicating nonautoimmune mechanisms.<sup>14</sup>

In persons with HIV infection, Graves disease may occur after immune reconstitution from HAART. A retrospective study found a median period of 20 months from initiation of HAART to the development of Graves' disease and a parallel increase of

CD4-cell count. This may be related to the resurgence of Th1 cytokine profile.<sup>15</sup> Transient Graves' disease has also been observed among HIV-infected patients with naïve CD4 cell expansion driven by IL-2 treatment.<sup>16</sup>

The most common thyroid function pattern during non-thyroidal illness is reduced T3 level, elevated reverse T3 (rT3) level, variable FT4 level, relatively normal/decreased thyroid stimulating hormone (TSH) level. However, some studies have shown that rT3 levels do not rise with decreasing T3 levels. Patients with progressive disease therefore, paradoxically have reduced T3 levels, decreased rT3 level, and increased TBG levels with increasing severity of illness.<sup>17</sup> During recovery from illness, the TSH levels may increase temporarily mimicking subclinical hypothyroidism. Among HIV-infected populations, non-thyroidal illness was seen in 16% of patients with terminal AIDS before the HAART era. AIDS-related conditions that cause thyroid dysfunction include thyroiditis due to *Pneumocystis jirovecii* infection, cryptococcus infection, visceral leishmaniasis, and suppurative bacterial infection of the thyroid.<sup>18</sup> Rarely, lymphoma and Kaposi sarcoma can infiltrate the thyroid and impair its function. CMV rarely causes thyroid disease. However in the HAART era, thyroiditis secondary to infectious etiology are rare.

Thyroid function testing in HIV infected patients should be done when symptoms of hypothyroidism or hyperthyroidism, osteopenia, dyslipidemia, depression, and atrial fibrillation are seen.

## Bone Loss

Reduced bone mineral density (BMD) is prevalent in primary HIV infection and may be associated with increased age, lower body mass index (BMI), lower TSH level, and higher levels of HIV-1 viremia.<sup>19</sup> Multiple cross-sectional studies have shown an increased prevalence of reduced BMD among HIV-infected individuals.<sup>20–22</sup> A systematic review revealed 6.4-fold increased odds of reduced BMD in HIV infected patients and 3.7-fold increased odds of osteoporosis compared to HIV uninfected controls.<sup>21</sup> A recent population based study confirmed a higher prevalence of bone fractures in HIV infected men and women compared to HIV uninfected controls.<sup>22</sup>

In ambulatory HIV positive men without wasting, BMD at the lumbar spine was marginally lower (3%) in ART naïve men than in age-healthy controls. The initiation of antiretroviral therapy results in significantly reduced BMD. Lumbar spine BMD was markedly lower in HIV positive men receiving PIs in comparison with HIV positives not receiving PIs and HIV negative controls.<sup>23</sup> However subsequent studies have given conflicting results.<sup>24</sup> Tenofovir (thymidine analog) has been reported to result in pronounced decline in BMD and may impair phosphate reabsorption in proximal renal tubules, resulting in osteomalacia.<sup>25</sup> Patients on long term treatment with antiretroviral therapy have been found to have stable BMD, suggesting that immunologic changes occurring during drug initiation may be contributory.<sup>26</sup>

Chronic HIV infection causes an increased synthesis of bone-resorbing TNF- $\alpha$ , IL-6 cytokines. These cytokines and viral proteins (Vpr, gp120) stimulate both osteoclast activity and decrease osteoclast apoptosis, thereby increasing bone resorption.<sup>27</sup> Most studies support the observation of increased bone turn over in HIV infected patients on ART. Serum levels of RANKL were significantly higher in HIV-positive men on ART in comparison to those who were not receiving ART. Serum osteocalcin decreases and C-telopeptide increases with advancing severity of HIV disease.

Low bodyweight, malnutrition, age, hypogonadism, drug abuse, drugs, alcohol, and smoking are other risk factors associated with bone loss.<sup>28</sup> Patients with advanced disease may have low 1,25(OH)<sub>2</sub>D levels due to impaired 1 $\alpha$ -hydroxylase activity.<sup>29</sup> Currently there are no firm recommendations for the treatment of osteoporosis for men or persons with HIV. Adequate intake of calcium and vitamin D should be part of any treatment regimen involving bone health.

## Electrolyte and Water Imbalance

Hyponatremia is the most commonly seen electrolyte abnormality in HIV-infected patients with a prevalence of 30–60% in hospitalized patients.<sup>30</sup> Hyponatremia has also been associated with increased mortality when compared to a normonatremic group. The usual outpatient cause of hyponatremia is diarrhea and vomiting. In hospitalized patients, the usual cause of hyponatremia is syndrome of inappropriate ADH secretion (SIADH), secondary to infectious causes related to pulmonary and neurological system.<sup>31</sup> Hypokalemia is commonly related to drugs used in the treatment of opportunistic infections. Amphotericin B and itraconazole are the usual causes. Tenofovir has been associated with Fanconi syndrome, hypokalemia, and nephrogenic diabetes insipidus.<sup>32</sup> Hyperkalemia is secondary to drugs like trimethoprim, foscarnet, and pentamidine used in the treatment of infectious pathogens.<sup>33</sup> The combination of hyperkalemia and hyponatremia occurs due to adrenal insufficiency or hyporeninemic hypoaldosteronism.<sup>34</sup> CMV has been reported to cause central diabetes insipidus by direct involvement of the AVP-producing neurons of the hypothalamus.<sup>35</sup>

## HIV-Associated Lipodystrophy

With antiretroviral therapy increased incidence of adverse effects including metabolic changes and pseudo-Cushing phenotype are observed. Lipodystrophy (LD) is a term used to describe these changes and it includes hyperlipidemia, insulin resistance, hyperglycemia, and characteristic phenotypic changes. There is loss of peripheral fat, resulting in characteristic facial appearance of sunken cheeks and thinning of extremities. Deposition of excess adipose tissue is seen around the neck, over the dorsocervical region resulting in buffalo hump, upper torso with supraclavicular hump, and infra-abdominal region simulating Cushing syndrome. In males, gynecomastia may be seen. Acanthosis nigricans is typically not seen and there is no significant weight loss or

opportunistic infection. These patients usually have relatively high blood CD4 counts with a lower level of viremia.<sup>36</sup>

There is no uniform agreement regarding the prevalence of LD in patients on HAART because of the differences in methodology and definition of LD. Different drug combinations further compound the problem with the result that prevalence has been reported to range from 10–80%. The usual time period for the onset of dyslipidemia and hyperinsulinemia or diabetes is weeks to months. Lipodystrophy manifests 10–18 months after initiation of drug therapy.<sup>37</sup> The frequency of LD varies with the drugs used. Nucleoside reverse transcriptase inhibitors (NRTIs), zidovudine and stavudine, have been associated with morphologic changes, especially extremity fat loss, while protease inhibitors (PIs) have been associated with insulin resistance or diabetes and dyslipidemia.<sup>38,39</sup> NRTIs such as stavudine have also been associated with dyslipidemia. Since the drugs are often used together as part of HAART, clinical data suggest that they act synergistically in causing LD. The body changes are distressing and the metabolic effects have been associated with an increased risk of cardiovascular disease.<sup>40</sup>

## Insulin Resistance and Diabetes

There is higher prevalence of type 2 diabetes in the HIV infected population without lipoatrophy or wasting when compared to an HIV seronegative cohort independent of HAART. The prevalence in patients on HAART is even higher. A cohort study reported an incidence of 7% of new-onset of diabetes based on 2-hour blood glucose >200 mg/dL after oral glucose tolerance test (OGTT).<sup>41</sup> Another recent study found the incidence of diabetes to be 4 times greater in HIV-infected men when compared to HIV-seronegative men.<sup>42</sup> Mulligan et al. found a direct role for PIs in causing insulin resistance (IR) and type 2 diabetes when HIV infected patients were initiated on PI-based HAART.<sup>43</sup> The association of PI-based therapy with IR and diabetes is well-established.<sup>44</sup> Nelfinavir and atazanavir are least associated with insulin resistance.

PIs are postulated to cause insulin resistance by inhibition of glucose transporter, GLUT-4.<sup>45</sup> These drugs vary in their ability to inhibit GLUT-4 with atazanavir showing no inhibition.<sup>46</sup> PIs also impair  $\beta$ -cell function and decrease first-phase insulin release.<sup>47</sup> Other contributing factors include increased lipolysis, induction of IL-6 and TNF- $\alpha$ , and reduction in gene expression and secretion of adiponectin.<sup>48,49</sup>

Patients with lipoatrophy have pronounced mitochondrial depletion as seen in biopsies from subcutaneous lipoatrophic tissues. Mitochondrial toxicity occurs through inhibition of mitochondrial DNA polymerase- $\gamma$  leading to lactic acidosis and organ toxicities including pancreas, liver, and muscle.<sup>50</sup> Fleischman et al. have shown that stavudine reduces insulin sensitivity with concomitant mitochondrial dysfunction in healthy volunteers.<sup>51</sup> A large prospective observational study of HIV-infected patients found that stavudine and zidovudine are significantly associated with diabetes after correction for lipids and risk factors for diabetes.<sup>52</sup> Among the NRTIs, tenofovir and lamivudine have

minimal effects on mitochondrial toxicity. Drug combinations in differing HAART regimens may act synergistically to cause mitochondrial toxicity.<sup>53</sup> The differences among drugs within the NRTI in causing mitochondrial dysfunction may probably be related to the varying affinities of the drugs for the mtDNA polymerase- $\gamma$ .

## Dyslipidemia

HIV-infected patients with or without AIDS prior to the HAART era have been reported to have lipoprotein abnormalities due to the acute phase response and inflammatory mediators. Early stage of HIV infection is usually associated with lower low density lipoprotein (LDL-C) and high density lipoprotein (HDL-C) levels. With advanced HIV and AIDS, triglycerides (TGL) levels are higher and LDL particles become smaller in density and more atherogenic.<sup>54</sup> With initiation of HAART, increases in total lipoprotein and LDL-C are observed. PIs are particularly associated with significant increase in TGL, total lipoprotein, and LDL-C levels. Elevation in TGL and total cholesterol are highest with ritonavir, lower with indinavir, nelfinavir, and amprenavir and lowest with saquinavir. HDL-C is usually lowered with PIs, with nelfinavir showing the least effect. Atazanvir, a new PI has been shown to have little effect on lipids.<sup>55</sup>

PIs cause direct inhibition of glucose uptake in adipocytes resulting in a significant reduction in TGL synthesis. This leads to adipocyte shrinkage and lipoatrophy. Sterol regulatory element binding proteins (SREBPs) which function as lipid sensors are activated and transported from endoplasmic reticulum (ER) to the nucleus where they promote synthesis of cholesterol and fatty acid biogenesis.<sup>56</sup> This results in excessive accumulation of intracellular cholesterol in ER inducing the ER stress response and accumulation of unfolded proteins which promote apoptotic cell death.<sup>57</sup>

HIV associated lipodystrophy increases the risk of cardiovascular disease as a result of dyslipidemia, insulin resistance, and diabetes mellitus. The clinical utility of metformin and the thiazolidinediones, rosiglitazone, and pioglitazone in treating HIV associated lipodystrophy patients is under investigation in terms of their effect on improving insulin sensitivity and reducing the progression from impaired glucose tolerance (IGT) to diabetes in non-HIV populations.<sup>58,59</sup> The first quantitative meta-analysis of randomized controlled trials evaluating the effects of rosiglitazone, pioglitazone or metformin on insulin, glucose, lipids, and body fat redistribution in patients with evidence of lipodystrophy has delivered mixed results of each of the insulin-sensitizing drugs. Rosiglitazone improved fasting insulin levels, but adversely affects fasting lipid levels and has no effect on central adiposity. Pioglitazone does not have any favorable effect on fasting insulin, plasma glucose, and central adiposity but improved HDL-cholesterol. Metformin had favorable outcomes in reducing fasting insulin, fasting TGL, and also in reducing central obesity. Adverse effects like lactic acidosis are not reported.<sup>60</sup> Currently, it seems metformin is the

insulin-sensitizer of choice which demonstrates beneficial effects on all three components of lipodystrophy.

## Conclusions

Subclinical adrenal insufficiency is common in HIV infection. In the advanced stages adrenal insufficiency occurs due to primary involvement of the gland or secondary to infections, drugs, and tumors. Lower basal cortisol and dehydroepiandrosterone levels are seen in the HIV infected. Shift to TH2 immunologic response; peripheral cortisol resistance, and drugs like protease inhibitors are the major contributing factors. Hypogonadotrophic hypogonadism as assessed by measuring free testosterone is seen in 20–50% of HIV-infected individuals. Alterations in thyroid function with raised TBG levels and low or raised free T4 can be seen. Subclinical hypothyroidism is common in HIV-infected individuals while Grave disease may occur during immune reconstitution syndrome. Low bone mineral density is seen frequently in HIV infected individuals due to various factors. Effects of antiviral agents is controversial. Most important electrolyte imbalance seen is hyponatremia, while potassium related complications are usually secondary to drugs.

HIV-associated lipodystrophy is observed in approximately 40–50% of ambulatory HIV-infected patients. The prevalence of insulin resistance and diabetes mellitus is increasing in HIV-infected patients with LD syndrome as the longevity is prolonged with effective drugs. The management of HIV/HAART-induced LD is complicated by the fact that almost all drugs have unacceptable adverse effects. Metformin with all its beneficial role in lipodystrophy has also been shown to result in peripheral fat loss, which can be cosmetically disfiguring.<sup>61</sup> Hence, the complexity of HAART coupled with limited studies on effective therapies, and significant potential for drug interactions necessitates large, well-controlled studies for better management of lipodystrophy and other metabolic complications.

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# AIDS Associated Malignancies and Their Treatment

Mark Bower • David Shackleton • Justin Stebbing

# 80

## Introduction

Acquired immunodeficiency syndrome (AIDS) following infection with human immunodeficiency virus (HIV), was brought to the world's attention in 1981 with the first case reports of *Pneumocystis carinii* pneumonia in homosexual men in Los Angeles.<sup>1</sup> These reports were quickly followed by descriptions of Kaposi sarcoma in similar patient groups.<sup>2,3</sup> There followed a cornucopia of opportunistic infections and isolated reports of high-grade B-cell non-Hodgkin lymphomas (NHL), both primary cerebral lymphomas and systemic NHL. By 1985 high-grade B cell NHL was included along with Kaposi sarcoma as an AIDS defining illness by the Centre for Disease Control (CDC) following the publication of series of 90 homosexual men with NHL.<sup>4-8</sup> A final AIDS defining malignancy, invasive cervical cancer was added as an AIDS defining illness in 1993, although the incidence of this malignancy is not increased as dramatically in HIV seropositive women.<sup>9</sup>

A number of other cancers occur at an increased frequency in people with HIV infection including Hodgkin disease, anal cancer, lung cancer, and testicular seminoma.<sup>10</sup> However, these malignancies have not been included in the definition of AIDS and they fall outside the scope of this chapter.

Dramatic improvements in the antiviral therapy of HIV infection occurred in the second half of the 1990s that have altered the natural history of HIV infection in those economies where these medicines are widely available. The introduction of highly active antiretroviral therapy (HAART) has led to a fall in the incidence of both opportunistic infection and AIDS associated malignancies.

## Highly Active Antiretroviral Therapy (HAART)

The development of effective antiretroviral therapies commenced with the introduction of nucleoside reverse transcriptase inhibitors starting with zidovudine in 1987. In the last decade, five new classes of antiretroviral agents have been introduced: protease inhibitors (e.g., saquinavir, indinavir, ritonavir, nelfinavir, lopinavir, atazanavir), non-nucleoside reverse transcriptase

inhibitors (nevirapine, delavirdine, efavirenz), non-nucleotide reverse transcriptase inhibitors (notably tenofovir), integrase inhibitors (raltegravir), and fusion inhibitors (enfuvirtide). The introduction of the first two classes in the late 1990s led to the use of combination HAART. HAART has had an enormous impact on the treatment of HIV in terms of overall survival, incidence of opportunistic infections, and quality of life. In randomized studies HAART leads to a dramatic decline in the mortality and morbidity of HIV.<sup>11</sup> However, only 1.5 million of the estimated 42 million people infected with HIV worldwide are receiving HAART as the majority of affected people live in developing countries.<sup>12</sup> In addition, even in the established market economies with access to medical treatment many individuals remain undiagnosed and consequently do not receive HAART. For the commonest AIDS-defining malignancy, Kaposi sarcoma, HAART remains an effective therapy<sup>13</sup> though its effect on lymphoma has been more controversial.<sup>14,15</sup>

## AIDS RELATED SYSTEMIC LYMPHOMA

### Epidemiology of AIDS Related Lymphoma in the Era of HAART

Non-Hodgkin lymphomas are associated with both congenital and iatrogenic immunosuppression and so it was perhaps not surprising that an increased incidence was demonstrated early in the AIDS epidemic. Registry linkage studies in the pre-HAART era found that the incidence of NHL in HIV positive individuals was 60–200 times higher than in the matched HIV negative population<sup>16,17</sup> and the relative risk was even greater for primary cerebral lymphomas.<sup>18</sup> Following the introduction of HAART the incidence of both Kaposi sarcoma and primary cerebral lymphoma has fallen significantly in both registry linkage and cohort studies,<sup>19-21</sup> this is thought to be secondary to the immune reconstitution that occurs with HAART.<sup>22,23</sup>

In contrast, the effects of HAART on systemic NHL are less clear<sup>24,25</sup> although some cohort studies suggest a modest nonsignificant decline in the incidence<sup>26</sup> including in the hemophilia population.<sup>27</sup> An international meta-analysis of 20



cohort studies compared the incidence of systemic NHL between 1992–6 and 1997–9. This meta-analysis confirmed an overall reduction in the incidence of both primary cerebral lymphoma (rate ratio = 0.42) and systemic immunoblastic lymphoma (rate ratio = 0.57) but not Burkitt lymphoma (rate ratio = 1.18).<sup>24</sup>

### Predictors of AIDS Related Lymphoma

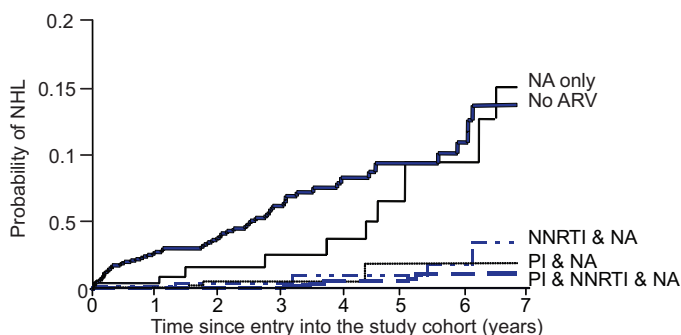
Genetic, infectious, and immunological factors influence the development of AIDS related lymphoma. For example, germ line chemokine and chemokine receptor gene variants have been found to influence the chance of developing these tumors. Aciclovir has mild activity against Epstein–Barr *in vivo* and one case-control study has shown that administration of high-dose acyclovir ( $\geq 800$  mg/d) for  $\geq 1$  year was associated with a significant reduction in the incidence of NHL.<sup>28</sup> However, data concerning the association between serum Epstein–Barr viral DNA loads and lymphoma development are controversial.<sup>29,30</sup>

In 2000, an analysis of our cohort of 7840 HIV positive patients, identified three factors in multivariate analysis that are significantly associated with the development of systemic NHL; age, nadir CD4 cell count, and no prior HAART. As the CD4 count falls, the development of lymphoma becomes more likely.<sup>14</sup> This may explain the declining incidence of NHL since the introduction of HAART as it is thought that the immune restoration that accompanies HAART protects against the development of AIDS related lymphoma.

These data were updated in 2004 using 9621 HIV-1 infected patients in our cohort. Here, it was again found that the use of HAART protected against NHL development. Moreover, nonnucleoside reverse transcriptase inhibitor (NNRTI)-based HAART (adjusted rate ratio, 0.4; 95% CI, 0.3–0.5) was as protective as protease inhibitor (PI)-based HAART, and these were significantly more protective than nucleoside analogs alone (rate ratio, 0.5; 95% CI, 0.4–0.7) or no antiretrovirals (Fig. 80.1;  $P < 0.001$ ).<sup>26</sup>

### Clinical Presentation of AIDS Related Lymphoma

The majority of patients with systemic AIDS related lymphomas present with advanced stage disease and B symptoms. Extranodal



**Fig. 80.1:** The probability of NHL and baseline exposure to different antiretroviral drugs over 7 years. ARV, antiretroviral therapy; NA, nucleoside analogue; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

disease, bone marrow involvement, and leptomeningeal disease are all common features. Hepatic involvement occurs in up to 25% patients while one in five patients has bone marrow involvement by NHL.<sup>8</sup> In addition, HIV infection itself is associated with trilineage abnormalities of hematopoiesis and the poor hematological reserves add to the myelotoxicity of cytotoxic chemotherapy.<sup>31,32</sup> Central nervous system involvement by systemic AIDS associated NHL is frequent; leptomeningeal disease is present at diagnosis in 3–10% and is significantly associated with Burkitt lymphoma and both bone marrow and paraspinal or paranasal involvement,<sup>33–35</sup> all of which necessitate intrathecal treatment.

In the published series from our institution that compared the clinical characteristics of 99 AIDS related lymphomas presenting prior to 1996 and 55 that presented between 1996 and 1999, there were no differences in the stage at presentation, presence of B symptoms, bone marrow infiltration, or performance status between the two groups. However, the patients who developed lymphoma in the HAART era were less likely to have had a prior AIDS diagnosis, were older, and had higher CD4 cell counts at the time of lymphoma diagnosis.<sup>14</sup> Thus although there has been a change in the immunological parameters of lymphoma patients, this would seem to reflect changes in the population at risk rather than any alteration of the biology of the lymphomas. A further analysis of patients who presented with lymphoma in the era of HAART compared those who were receiving HAART at the time of lymphoma diagnosis ( $n = 17$ ) with those who were not ( $n = 34$ ). Again there were no significant differences between the stages or disease sites at presentation but the CD4 cell counts at lymphoma diagnosis were higher in those on HAART.

### Treatment of AIDS Related Lymphoma in the Era of HAART

During the 1980s, conventional chemotherapy schedules were used at full dosages for patients with better prognostic factors. However, marked toxicity and an increased incidence of opportunistic infections lead to modifications of the standard lymphoma regimens. The subsequent development of hematopoietic growth factors allowed more myelotoxic schedules to be studied. The appreciable death rate from opportunistic infections generally offset any decline in NHL related deaths and most centers persisted with either dose reduced chemotherapy schedules or prognostic stratification that reserved full dose therapy for patients with the best prognostic factors only.<sup>36</sup>

Recently, a number of groups have described an improvement in the overall survival compared to historical controls since the introduction of HAART. The complete remission rate and overall survival with CHOP chemotherapy has improved with the addition of HAART to the chemotherapy<sup>36,37</sup> and the goal of therapy is clearly complete remission, not palliation.<sup>38</sup> However, in other series there has been no change in the lymphoma response rates and the improvements in survival duration may be related to reduced deaths from opportunistic infections among patients who achieve durable tumor remissions.<sup>39–41</sup> Nonetheless these

encouraging findings have lead to a more aggressive approach to the management of AIDS associated NHL.

Infusional chemotherapy for high-grade lymphoma was pioneered at the Albert Einstein Cancer Centre in New York using the combination of cyclophosphamide, doxorubicin, and etoposide (CDE) administered as a 96 hour continuous infusion together with granulocyte colony stimulating factor (G-CSF).<sup>42</sup> Early reports of a selected group of 25 patients with AIDS related lymphomas who were treated with CDE and didanosine produced an impressive median survival of 18.4 months and was widely heralded as a breakthrough.<sup>43</sup> The same schedule was then combined with saquinavir, with similar results although there was more mucositis with the protease inhibitor. A large multicenter phase II trial of infusional CDE has been conducted by the Eastern Cooperative Oncology Group and the results have been far less impressive as is so often the case following encouraging initial single center studies.<sup>44</sup>

In our cohort, 56 patients with systemic AIDS-related non-Hodgkin lymphoma (ARL) were treated with concomitant HAART and infusional CDE chemotherapy. We compared neutropenia according to whether patients received protease inhibitor PI-based HAART or non-PI regimens. Differences in survival, response rates, immunologic parameters, and virologic parameters were also investigated. The day-10 (Mann-Whitney U test;  $P = 0.012$ ) and day-14 ( $P = 0.025$ ) neutrophil counts were significantly lower in patients receiving PIs, though there were no differences in the number of days of granulocyte colony-stimulating factor (G-CSF) administered between groups ( $P = 0.16$ ). Grade 3 or 4 infections requiring hospitalization were recorded for a total of 58 (31%) of 190 cycles of CDE: 23 (48%) of 48 when prescribed PIs and 35 (25%) of 142 with concomitant PI-sparing HAART ( $P = 0.0025$ ). There were no statistically significant differences in the response rates, relapse-free survival, or disease-free survival between patients receiving PIs and those not receiving PIs. PI-based HAART appears to significantly potentiate the myelotoxicity of CDE chemotherapy.<sup>45</sup>

At the National Cancer Institute, EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin), a dose-adjusted schedule has been developed which omits all HAART for the duration of the chemotherapy. Initial reports have been encouraging with a complete response rate of 79%. However, there was a dramatic fall in CD4 cell count during chemotherapy and even with restarting the HAART at the end of the chemotherapy; this took 12 months to recover to baseline levels.<sup>46</sup> This phase II study has been expanded to 39 selected patients now<sup>47</sup> and EPOCH is currently under investigation in a multicenter study. As there are no comparative studies, it is difficult to recommend an optimal gold standard therapy and there are advocates of conventional CHOP as well as supporters of infusional therapies.

The high rate of leptomeningeal disease at presentation, which may be asymptomatic led to the widespread use of staging lumbar punctures and prophylactic intrathecal chemotherapy for patients

considered to be at high risk of relapse in the cerebrospinal fluid. The prophylactic administration of intrathecal chemotherapy to patients with these risk factors but without meningeal disease at presentation prevented meningeal relapse in 81%.<sup>48</sup>

Chemotherapy results in a decline in CD4 cell counts in both the immunocompetent and immunocompromised and prophylaxis to prevent opportunistic infections particularly in this patient group requires careful attention. It is well-established in the management of HIV infection that prophylaxis against *Pneumocystis carinii* pneumonia should commence when the CD4 cell count falls below 200/mm<sup>3</sup> and against *Mycobacterium avium* complex when it falls below 50/mm<sup>3</sup>.<sup>49,50</sup>

The prolonged T cell depletion recorded following EPOCH was previously demonstrated for patients receiving chemotherapy in the pre-HAART era.<sup>51</sup> The concomitant use of chemotherapy and HAART has been widely practiced and when used together the CD4 cell count declines by 50% during chemotherapy but recovers rapidly within 1 month of completing chemotherapy. The CD8 and natural killer (CD16 and CD56) cell counts follow a similar profile while the B cell (CD19) count recovers more slowly but is restored to prechemotherapy levels by 3 months. There was no change in the HIV mRNA viral load during the chemotherapy.<sup>52</sup> In view of the decline in CD4 cell count by 50%, PCP prophylaxis should commence at CD4 cell counts of 400/mm<sup>3</sup> and MAC at CD4 counts of 100/mm<sup>3</sup>.

The improved survival described since the introduction of HAART and the preservation of immune function suggests that the combination of chemotherapy with HAART is an important step forward in the management of AIDS related lymphomas. However, there are both toxicity and pharmacokinetic drawbacks to the concomitant administration of chemotherapy and HAART. For example, the potentiation of myelotoxicity with CDE combined with protease inhibitors may be a consequence of microsomal enzyme inhibition reducing the metabolism of cytotoxics in this regimen.<sup>45</sup>

## Outcomes in the Era of HAART

The complete remission rates for regimens using the combination of chemotherapy and HAART are 48–92% and the published 2 year overall survivals are 48–60%.<sup>53–58</sup> These response rates and survival duration statistics are starting to approach those seen in the general population with advanced stage high-grade lymphoma. Indeed while the prognostic factors for survival in the pre-HAART era were predominantly immunological (prior AIDS defining illness and CD4 cell count) a more recent analysis of prognostic factors in AIDS related lymphoma closely resembles that for the general population with the international prognostic index being an equally valuable guide in both circumstances.<sup>59</sup> Recent data from our institution suggests the CD4 count to be an independent prognostic variable too, and a prognostic model has been established based solely on international prognostic index (IPI) scores and CD4 cell counts.

## Future Developments for AIDS Related Lymphomas

The improvements in the treatment of HIV infection have led to a more aggressive management strategy for AIDS related lymphomas and this has resulted in better outcomes. Further refinements mirror those seen in immunocompetent patients with high-grade lymphoma including the addition of anti-CD20 antibodies to first-line therapy and the use of high-dose chemotherapy with autologous stem cell transplantation at first relapse. Rituximab in addition to chemotherapy has yielded increased response rates (70% complete response with a 59% 2 year survival).<sup>36</sup> Patients have also undergone successful autologous stem cell transplantation for AIDS related lymphomas despite predictions that adequate harvesting would prove difficult on account of myelodysplasia.<sup>60–63</sup>

## PRIMARY CEREBRAL LYMPHOMA

Primary central nervous system lymphoma (PCL) is defined as non-Hodgkin lymphoma that is confined to the craniospinal axis without systemic involvement. This diagnosis is rare in immunocompetent patients but occurs more frequently in patients with both congenital and acquired immunodeficiency. AIDS related PCL occurs equally frequently across all ages and transmission risk groups and the tumors are high-grade B-cell diffuse large cell or immunoblastic non-Hodgkin lymphomas. The presence of Epstein–Barr virus is a universal feature of HIV-associated PCL but EBV is not found in other PCL.<sup>64</sup> EBV may be detected by immunocytochemical staining of biopsy tissue or by polymerase chain reaction (PCR) amplification of cerebrospinal fluid (CSF) using EBV specific oligonucleotide primers.<sup>65,66</sup>

## Epidemiology

Registry linkage studies confirmed a markedly increased relative risk of PCL among patients with AIDS with an incidence as high as 2–6% in one early report.<sup>67</sup> This vastly elevated incidence of PCL was confirmed by both cohort and linkage studies. Patients who developed PCL generally have advanced immunosuppression and for the most part have had a prior AIDS defining illness. Shortly after the introduction of HAART a decline in the incidence of PCL was recognized by many clinicians and a meta-analysis of cohort studies that compare the pre and post HAART eras confirmed a significant decline (relative risk 0.42: 99% confidence interval 0.24–0.75).<sup>24</sup> Indeed this fall is more dramatic than that seen for systemic AIDS related lymphomas and PCL is associated with more severe immunosuppression than systemic AIDS related lymphoma.

## Clinical Presentation and Differential Diagnosis

The commonest causes of cerebral mass lesions in HIV seropositive patients are toxoplasmosis and primary cerebral lymphoma and the differential diagnosis often proves difficult.<sup>68</sup> Both diagnoses

occur in patients with advanced immunodeficiency (CD4 cell counts  $< 50 \times 10^6/L$ ) and present with headaches and focal neurological deficits. Clinical features that favor PCL include a more gradual onset over 2–8 weeks and the absence of a fever. CT and MRI scanning usually reveal solitary or multiple ring enhancing lesions with prominent mass effect and edema. Again these features occur in both diagnoses although PCL lesions are usually periventricular while toxoplasmosis more often affects the basal ganglia. Thus, the combination of clinical findings and standard radiological investigations rarely provide a definitive diagnosis. Moreover, toxoplasma serology (IgG) is falsely negative in 10–15% of patients with cerebral toxoplasmosis. More than 85% patients with cerebral toxoplasmosis will respond clinically and radiologically to 2 weeks of antitoxoplasma therapy and this has become the cornerstone of the diagnostic algorithm for cerebral masses in severely immunodeficient patients.

In these patients it has been standard practice to commence empirical antitoxoplasmosis treatment for 2 weeks duration, and resort to a brain biopsy if there is no clinical or radiological improvement. This strategy avoids the routine use of brain biopsy in these patients who frequently have a very poor performance status and prognosis. Although this algorithm avoids early surgical intervention, it is relatively ineffective in diagnosing PCL early, and may compromise the outcome of therapy in these patients. In addition, there is a disinclination to treat patients with radiotherapy or chemotherapy empirically based exclusively on the failure of antitoxoplasmosis treatment without a definitive histological diagnosis.

The discovery that all HIV-associated PCL are associated with EBV infection has led to the development of a PCR method that can detect EBV-DNA in the CSF. This has become established as a diagnostic test with a high sensitivity (83–100%) and specificity ( $>90\%$ ).<sup>69,70</sup> In addition, radionuclide imaging by <sup>201</sup>Thallium single photon emission computed tomography (<sup>201</sup>Th-SPECT) or <sup>18</sup>Ffluorodeoxyglucose-positron emission tomography (FDG-PET) is able to differentiate between PCL and cerebral toxoplasmosis. PCL are thallium avid and demonstrate increased FDG uptake on PET scanning, however although both techniques have high specificity for PCL neither are highly sensitivity and thus cannot be used alone but in combination with PCR are emerging as a diagnostic alternative to brain biopsy. The application of PCR and <sup>201</sup>Th-SPECT in the diagnosis of contrast enhancing brain lesions in 27 patients was shown to result in a positive and a negative predictive value of 100% and 88%, respectively, which supports their combined value as an alternative to brain biopsy.<sup>71</sup> Further studies are now required to compare effectiveness of PCR with <sup>201</sup>Th-SPECT or FDG-PET.

## Treatment

The standard treatment modality of PCL is whole brain irradiation but the median survival time is just 2.5 months or less. Although patients who were treated with radiotherapy or chemotherapy



lived longer than those who received best supportive care only, no randomized studies have been conducted and it remains uncertain whether therapy improves survival.<sup>72</sup> There is increasing enthusiasm for the treatment of PCL in immunocompetent patients with both radiotherapy and chemotherapy and recent results have been encouraging. The use of chemotherapy for PCL is limited by the poor penetration of cytotoxics into brain parenchyma on account of the blood brain barrier and the toxicity especially myelosuppression of these agents in patients with advanced immunosuppression and poor performance status. Combination chemotherapy prolongs survival in immunocompetent patients with PCL but at the cost of severe myelotoxicity. Single agent chemotherapy with intravenous high-dose methotrexate and folinic acid rescue was studied in AIDS patients with PCL in the context of a prospective uncontrolled study which included 15 patients. The results showed a complete response in 47% of patients, a median survival of 19 months; a low relapse rate of approximately 14% and no evidence of neurological impairment nor treatment limiting myelotoxicity.<sup>73</sup> A controlled trial of intravenous methotrexate versus whole brain irradiation is needed to confirm these encouraging results. Now that antiretroviral therapies are improving survival it may be necessary to reassess currently available diagnostic and treatment modalities aiming to cure HIV-associated PCL.

One intriguing development is the description of tumor regression of PCL with HAART therapy alone.<sup>74</sup> These case report observations require confirmation in cohort studies but in our experience very few patients with HIV-associated PCL are HAART naïve at the time of diagnosis of PCL.

## KAPOSI SARCOMA (KS)

### Epidemiology, Virology, and Pathogenesis

Soon after the first events of the HIV epidemic, the New York Times headline “Rare cancer seen in 41 homosexuals” referred to cases of KS. This aggressive and frequently fatal epidemic variant of KS affected homosexual men with AIDS approximately 20 times as frequently as male patients with hemophilia and AIDS who had similar degrees of immunosuppression.<sup>75–79</sup> Although the incidence of KS in American men with AIDS decreased from 40% in 1981 to less than 20% in 1992, today it remains the most common AIDS-associated cancer in the United States and an important cause of morbidity and mortality, particularly in sub-Saharan Africa.<sup>80–87</sup>

While a total of four clinical variants of KS have now been described, known as classical, endemic, iatrogenic (post-transplant), and epidemic (AIDS-associated) forms,<sup>88</sup> in the light of recent discoveries regarding the viral pathogenesis of KS, these variants are thought to represent different manifestations of the same pathologic process.<sup>89</sup>

It was noted early in the HIV pandemic that AIDS associated KS was more prevalent in gay men than in other transmission groups and this observation led Valerie Beral and Harold Jaffe to propose that a second infectious agent could account for the

prevalence of KS in immunodeficient patients.<sup>77,90</sup> In 1994 Chang and colleagues used representational difference analysis to identify DNA fragments of a previously unrecognized herpesvirus, which they called Kaposi sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus-8).<sup>91</sup> This was the second oncogenic virus after human papillomavirus, to be identified by molecular techniques. Soon after, KSHV was implicated in the etiopathology of primary effusion lymphoma (PEL)<sup>92</sup> and multicentric Castleman disease (MCD),<sup>93,94</sup> the management of which will be discussed later. Although studies have been published on the contribution of cytokines as well as HIV-1 Tat protein in the pathogenesis of KS, the presence of KSHV is a necessary factor in the development of this tumor and it can be found in every KS lesion, at every stage of its development. In addition, immunosuppression in the host appears to be an important cofactor in the clinical expression of KS in KSHV-infected individuals.<sup>95</sup>

The 165 Kb KSHV genome was sequenced within 2 years of the virus’ discovery and it provided initial clues about the way in which this virus might induce uncontrolled cellular proliferation.<sup>96</sup> Unusual to KSHV (among the herpes viruses) and its newly discovered primate cousins is the very large number of genes encoding homologs of host genes.<sup>97–105</sup> For example, KSHV encodes a homolog of cyclin D2 whereas the related gamma-herpesvirus EBV LMP-1 induces cyclin D2 in B-cells (which normally do not express this protein).<sup>106</sup> It is thought that the acquisition of host genes may enable KSHV to utilize many host cellular processes and avoid antiviral responses. The virus encodes proteins that are homologous to human oncoproteins, including another cyclin that inhibits the retinoblastoma protein, which controls the G1-to-S phase of cell growth, and a Bcl-2-like protein that prevents apoptosis.<sup>107–110</sup>

KSHV also encodes a viral homolog of interleukin-6 (vIL-6), which is thought to act in a paracrine manner and stimulate a local acute phase response. Increased levels of IL-6 are found in tissues affected by KSHV and IL-6 is thought to be an important growth factor in not only KSHV driven neoplasms<sup>111–114</sup> but also in lymphomas driven by Epstein–Barr virus.<sup>115,116</sup> As such, there are data that suggest that KS is not a clonal neoplasm per se but begins as a localized inflammatory response.<sup>117</sup>

### Clinical Features

The first cases of KS described in 1872 were observed to be “idiopathic pigmented multiple sarcomas of the skin”.<sup>118</sup> AIDS related KS exhibits a wide spectrum of clinical presentations and some patients may have few lesions, others many—these sometimes develop rapidly.<sup>82</sup> The earliest cutaneous lesions are frequently asymptomatic innocuous looking macular-pigmented lesions, which vary in color from faint pink to vivid purple. Larger plaques occur usually on the trunk as oblong lesions following the line of skin creases. Lesions may develop to form large plaques and nodules that can be associated with painful edema. Lymphatic infiltration is a common feature in the limbs and causes lymphedema and ulceration.

Oral lesions are a frequent accompaniment that may lead to ulceration, dysphagia, and secondary infection while gastrointestinal lesions are usually asymptomatic but may bleed or cause obstruction. Pulmonary KS is a life threatening complication that usually presents with dyspnea and a dry cough with or without fever and may cause hemoptysis. Chest radiographs typically reveal a diffuse reticulonodular infiltrate and pleural effusion. The main differential diagnosis of cutaneous KS is bacillary angiomatosis, a feline zoonosis caused by *Bartonella henselae*, a fastidious gram-negative bacterium of the Rickettsia family.<sup>119–121</sup>

## Treatment of KS

The prognosis of patients with KS depends upon both the stage of the KS, the level of immunosuppression, and the response to anti-HIV therapy.<sup>122</sup> KS is staged using the AIDS clinical trials group modified staging classification (see Table 80.1). For patients with symptomatic disease or life threatening visceral disease prompt effective therapy is usually merited, while for patients with asymptomatic indolent lesions HAART alone may result in complete regression.

## Highly Active Antiretroviral Therapy

Current data suggests that there has been a fall in the incidence of KS both as a first AIDS diagnosis and a subsequent manifestation in HIV seropositive cohorts from established market economies. This decline in KS coincides with the introduction of HAART and in some cohort studies the relative risk of developing KS is significantly lower among people receiving HAART regimens.<sup>21,25,124–126</sup> A large number of case reports and small studies documenting responses of KS to HAART have been published and regression of KS during monotherapy with zidovudine has also been observed.<sup>127</sup>

A cohort study of 78 patients with established KS has demonstrated that the introduction of HAART therapy is associated with a prolongation of the time to treatment failure of KS (log rank  $\chi^2=16.5$ ,  $P < 0.0001$ ).<sup>128</sup> Thus HAART therapy has a major influence both on the epidemiology and clinical progression of KS without apparently having a direct effect upon the causative herpesvirus, KSHV. The lower incidence and regression of KS observed with HAART may result from a

variety of effects but is likely to include immune reconstitution following HAART with increased natural killer and cytotoxic T lymphocyte activity.<sup>129</sup>

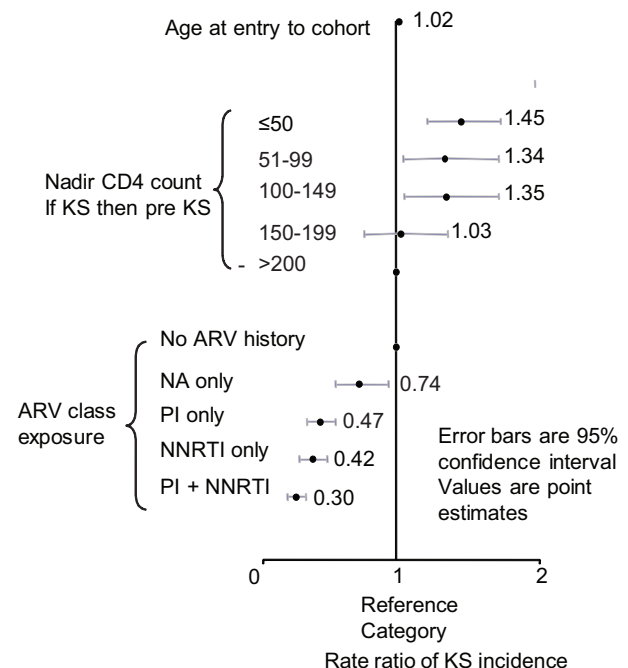
As protease inhibitors have been suggested in some studies to have specific antiangiogenic and thus anticancer activity,<sup>130</sup> we compared antiretrovirals to determine whether their anti-KS effects were largely confined to PIs. Multivariate logistic regression analyses of 1204 cases of AIDS-KS seen between 1986 and 2002, found that the incidence decreased from 30 cases per thousand patient years (PY) prior to 1995 to 7.6 immediately thereafter. This was clearly coincident with treatment using dual nucleoside analog reverse transcriptase inhibitors. More recently the incidence has fallen dramatically to 0.03 cases per thousand patient years, although to our surprise patients receiving non-PI based therapies had a statistically significant difference in their incidence of KS when compared with those treated with PIs: 0.2 cases per 1000 patient years (95% CI 0.02–0.12) versus 1.1 cases per 1000 patient years (95% CI 0.15–0.38), respectively, ( $P = 0.002$ ).<sup>21</sup> This study, the first showing a decreased incidence of an AIDS defining illness with NNRTI based therapy, demonstrates that non-PI based regimens are at least as effective as PI-based HAART in terms of protection against KS (Fig. 80.2).

We have also found lack of correlation with angiogenic markers as measured by ELISA to response and overall these data further implicate the immune system in tumorigenesis.<sup>131</sup> As many cases of KS do not resolve with HAART alone or are considered 'too aggressive' for HAART, cytotoxic chemotherapy is often used to induce responses.

A proportion of individuals with human immunodeficiency virus infection (HIV) who subsequently receive HAART

**Table 80.1:** The Modified AIDS Clinical Trials Group Staging of KS (1997)<sup>123</sup>

	Good risk (all of the following) T0 I0	Poor risk (any of the following) T1 I1
Tumor (T)	Confined to skin, lymph nodes, or minimal oral disease	Tumor-associated edema or ulceration Extensive oral KS Gastrointestinal KS KS in other non-nodal viscera
Immune status (I)	CD4 count $>150/\mu\text{L}$	CD4 $<150/\mu\text{L}$



**Fig. 80.2:** Multivariate log linear model showing significant independent predictors of KS during the HAART era.

exhibits deterioration in their clinical status, despite control of virologic and immunologic parameters. This clinical response, known as the immune reconstitution inflammatory syndrome (IRIS) occurs secondary to an immune response against previously diagnosed pathogens. Occasional case reports of this phenomenon occurring for KS have been presented. We studied a cohort study of 150 patients with HIV-associated KS starting HAART for the first time as sole treatment for the KS. After commencing HAART, ten of these patients (6.6%) developed progressive KS which we identified as IRIS-associated KS. IRIS-KS occurred in patients with higher CD4 counts ( $P = 0.03$ ), KS associated edema ( $P = 0.01$ ) and therapy with both protease inhibitors and non nucleosides together ( $P = 0.03$ ). Time to treatment failure was similar for both groups, although the CD4 count declined more rapidly at first, in those with IRIS-associated KS. Despite this initial decline, in our clinical experience HAART could be successfully continued in those with IRIS-associated KS.<sup>132</sup>

## Chemotherapy for KS

### Liposomal Anthracyclines

Liposome encapsulation of anthracyclines constitutes a considerable advance in the chemotherapy of KS. The advantages of liposomal formulation include increased tumor uptake and hence favorable pharmacokinetics.<sup>133–138</sup> Moreover, the liposomal forms are less cardiotoxic than the parent anthracyclines. Both liposome encapsulated daunorubicin (Daunoxome 40 mg/m<sup>2</sup> every 2 weeks) and the pegylated liposomal doxorubicin (Caelyx 20 mg/m<sup>2</sup> every 3 weeks) have been shown to have good antitumor activity. The toxicity profile is better than for other anthracyclines, with no reported cardiotoxicity even with high cumulative dosages and rarely significant alopecia; however there remains considerable myelosuppression, and occasional emesis.

In addition, infusion related hypotension and hand/foot syndrome are novel side effects seen with these liposomal formulations. In randomized comparisons of liposomal doxorubicin compared to other chemotherapies as first-line therapy for KS, response rates were higher liposomal doxorubicin arm.<sup>139–141</sup> Liposomal anthracyclines are considered first-line chemotherapy for advanced KS.

### Paclitaxel

Paclitaxel has been shown to have single agent activity against KS and has a valuable role in the management of refractory disease. The toxicities of paclitaxel are well-recognized, although appear to be no worse in patients with HIV than in other groups treated with equivalent dosages. Two studies of refractory KS have shown response rates of 53% and 71% and median response durations of 7.4 and 10.4 months.<sup>142,143</sup> These results have led to the rapid acceptance of paclitaxel (100 mg/m<sup>2</sup> over 3 hours every 2 weeks) as the treatment of choice for anthracycline refractory KS.<sup>131,142</sup>

Unsurprisingly, weekly docetaxel has also been shown to be safe and effective in a small phase 2 study.<sup>144</sup>

### Other Agents and Radiotherapy

A number of other chemotherapeutic agents have demonstrated activity against Kaposi sarcoma. These include etoposide, bleomycin, and vincristine.<sup>145,146</sup> Localized therapies are advocated for patients with limited non-life threatening cutaneous disease. An intralesional injection of a dilute solution of vinblastine (0.2 mg/ml) using volumes of up to 0.5 ml per lesion is an effective, easy, and well-tolerated treatment for lesions under 1 cm in diameter. Intralesional vinblastine has no significant systemic effects and injections may be repeated 2 or 3 times. This approach is also valuable for small intraoral lesions and gingival lesions. The United States Food and Drug Administration has recently approved 0.1% 9-cis-retinoic acid gel as a topical treatment for AIDS-related KS based on one vehicle-controlled trial. Here, 35% of patients who received a 12-week course of the gel and 18% of patients treated with the vehicle gel demonstrated an objective response ( $P = 0.002$ ).<sup>147</sup> Application site reactions (i.e., erythema, bruising, flaking) were common but rarely severe.<sup>148,149</sup> Additional topical treatments available include liquid nitrogen.

Larger cutaneous or oral lesions may be treated with radiotherapy and local control is generally achieved. For cutaneous lesions either a single fraction of 8Gy or 16Gy in four fractions is routinely used. Although the response rate and duration of local control may be better with fractionated regimens compared with single fraction treatment, toxicity and patient convenience are worse. Cosmetic improvement is usually achieved although there may be a halo appearance on account of the margin around treated lesions. Severe mucositis and acute edema reactions may follow radiation treatment of the oral cavity and feet and for this reason treatment is given in four fractions at weekly intervals. Recurrent tumor is common and therefore radiotherapy treatment is usually reserved for symptomatic and cosmetically disturbing lesions.<sup>150</sup>

## Future Developments for AIDS-Related Kaposi Sarcoma

KS has been recognized as a clinical entity for well over a century and has been a known complication of HIV infection for 3 decades. It is only in the last few years since the discovery of KSHV as its causative agent that the multiplicity of factors in its pathogenesis is being unravelled. A wide variety of treatments appear able to inhibit KS growth including antiretrovirals, cytotoxic chemotherapeutic agents, retinoids, thalidomide, and inhibitors of matrix metalloproteinases. There is also considerable interest in evaluating the role of antiherpes drugs for KS. The role of interferon- $\alpha$ , both pegylated and nonpegylated forms are being established in clinical trials following significant evidence of antineoplastic and antiviral activity *in vitro*.

An improved understanding of the functions of the KSHV genes, the identification of novel immune-evasion strategies and



the analysis of the KS microenvironment in the context of a viral infection, should lead to a better understanding of angiogenesis, the immune system, and the interaction of viruses with their hosts. This will help us to design safer strategies to treat virus-induced pathology. As many cases of KS do not resolve with HAART and require treatment with cytotoxic chemotherapy, it is also important to reveal the underlying mechanisms involved in the response to treatment.

## CERVICAL CANCER

### Epidemiology

Invasive cervical cancer was included as an AIDS defining diagnosis in 1993, although the incidence of cervical cancer was not then increased significantly in HIV seropositive women.<sup>9,151</sup> Nonetheless there is good epidemiological evidence that the precursor lesions, cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesion (SIL) occur more frequently in women with HIV.<sup>152</sup> Human papillomavirus (HPV) has a central role in the pathogenesis of both CIN and invasive cervical cancer. HIV is associated not only with a higher prevalence of HPV in the cervix, a high frequency of multiple HPV genotypes and persistence of HPV in the cervix, but also a higher prevalence of CIN/SIL, a higher progression from low-grade SIL to high-grade SIL, and a greater likelihood of relapse of CIN II/III after therapy. The risk of SIL is greatest among women with CD4 cell counts <200 cells/mm<sup>3</sup>. These findings mandate close colposcopic surveillance.<sup>153</sup>

### Effects of HAART on Pre-invasive Cervical Cancer

The effect of HAART on the natural history of CIN has been addressed in women with advanced HIV. Five months after starting HAART the prevalence of CIN fell from 66% to 49%, regression of HGSIL to LGSIL occurred in 23% and from LGSIL to normal in 43%. These changes occurred without a significant change in the level of HPV DNA in cervical tissue.<sup>154</sup> In a recent women's interagency HIV study (WIHS) cohort from 5 US cities, the effect of HAART on CIN was assessed by 6 monthly smear testing. After adjustment for CD4 cell count and Papanicolaou smear status, women on HAART were 40% (95% confidence interval, 4–81%) more likely to demonstrate regression and less likely (odds ratio, 0.68; 95% confidence interval, 0.52–0.88) to demonstrate progression.<sup>155</sup> However the benefits of HAART have not been reproduced in all studies and HAART appears to have limited ability to clear HPV infection and induce regression of CIN in HIV-positive women. Current data suggest that frequent cervical smears should be offered to all HIV positive women and that CIN should be aggressively treated in these women.

### Invasive Cervical Cancer Management

In most centers HIV seropositive women with invasive cervical cancer are treated using the same protocols as immunocompetent

women. One retrospective series compared 28 HIV positive women with 132 seronegative women treated at the same institution and time period. The results demonstrated that women with HIV had more advanced cervical cancer at presentation.<sup>156</sup> A similar case control study from the same institution demonstrated that women with cervical cancer who were HIV seropositive relapsed more frequently and had a worse median survival.<sup>157</sup> Although there is hope that the survival of invasive cervical cancer may improve with the introduction of HAART, there is scant data to support this optimism.<sup>158</sup>

As HPV also causes anal intraepithelial neoplasia (AIN), the precursor lesion for anal cancer, we have examined whether effective HAART leads to regression of AIN. Results were inconclusive<sup>159</sup> although we did find in 99 men that anal cytology by the Palefsky method is simple to undertake, has a sensitivity and specificity comparable with cervical cytology, and can therefore be used as the basis of a pilot screening project in centers with large cohorts of HIV positive homosexual men who have a high risk of developing anal carcinoma.<sup>160</sup> Unlike other HIV-associated cancers, there has been no significant change in the incidence, clinical features, or overall survival since the introduction of HAART.<sup>161</sup>

### Primary Effusion Lymphoma (PEL)

PEL is an unusual lymphoproliferative disorder, accounting for 2% or less of HIV-associated lymphomas, and is even more rarely encountered in the HIV-seronegative patient. PEL is divided into classic and solid variants. Classic PEL is characterized by lymphomatous involvement of the serosal surfaces, whereas solid PEL manifests initially with tissue-based tumors and no malignant effusions.<sup>162,163</sup> They are similar by morphology, immunophenotype, and molecular analysis. KSHV along with high levels of interleukin (e.g., IL-6) may be found in PEL tumor cells and this is frequently necessary to aid in the diagnosis. The ramifications of large and typically recurrent pleural, pericardial, and peritoneal effusions are grave and are responsible for the high morbidity and mortality associated with this condition.<sup>164</sup>

PEL cells have a characteristic phenotype highlighted by CD45, CD30, CD38, CD138, and MUM1 coexpression.<sup>162</sup> Classic B-cell markers (CD19, CD20) and T-cell markers (CD2, CD3, CD5, CD7) are not typically seen. Gene expression profiling has shown that PEL expresses a gene profile distinct from other lymphomas, but more akin to multiple myeloma cell lines.

There is no clear standard of care established in the treatment of PEL, and due to its low incidence, randomized clinical trials at present are not feasible. As with the other KSHV-associated diseases, if HIV coinfection is identified, antiretroviral therapy is critical. Spontaneous regression with the commencement of HAART has been described.<sup>165</sup> Traditionally, the use of standard cytotoxic regimens used for non-Hodgkin lymphomas are suboptimal, and median survival in treated cohorts is poor. Induction of apoptosis with the inhibition of NF-κB in PEL cell

lines has led to the investigation of proteasome inhibitors which decreases the activation of NF- $\kappa$ B and its antiapoptotic effects.<sup>166</sup> Bortezomib, a proteasome inhibitor that is FDA approved in the USA for use in multiple myeloma, has been shown to enhance the *in vitro* cytotoxic effects of doxorubicin and paclitaxel, and has been used successfully in combination with anthracycline-based cytotoxic chemotherapy regimens. Inhibition of mTOR with rapamycin is effective at decreasing *in vitro* PEL growth and *in vivo* mouse xenograft model tumor growth, and its increasing use in the treatment of PEL can be foreseen.<sup>167</sup> Cases of prolonged survival in persons treated adjunctively with antiviral therapy (ganciclovir or cidofovir) have also prompted the adjunctive use of these drugs in PEL. Valproate to treat PEL induces lytic KSHV replication and leads to apoptosis in combination with antiviral agents.

### Multicentric Castleman Disease (MCD)

MCD is a rare lymphoproliferation and we have calculated that in the HAART era it has an incidence of 4.3/10,000 patient years.<sup>168</sup> MCD is an aggressive lymphoproliferative disorder, characterized by constitutional symptoms, anemia, and generalized lymphadenopathy. Small series have shown that most MCD cases are driven by KSHV, including 100% of HIV-seropositive patients and the majority of HIV-negative patients.<sup>169</sup> The failure to identify KSHV in all MCD lesions may either reflect technical limitations in KSHV detection, the ability for KSHV to induce MCD distant to the biopsied tissue, or an alternate etiology for a limited number of cases. On occasion, MCD may be associated with non-Hodgkin lymphoma, particularly the plasmablastic variant. A key to making the diagnosis is to suspect MCD in high-risk individuals who present in the appropriate clinical context (i.e., immunosuppressed individual with KSHV infection or other KSHV associated disease). Definitive diagnosis can only be made by pathologic examination of an involved lymph node or extranodal mass. Detection of KSHV in biopsied tissue or in the peripheral blood can aid in the diagnosis. C-reactive protein, KSHV viral load, and serum IL-6 levels, if available, may be useful as markers of disease activity and response to therapy.<sup>170</sup>

In patients with MCD and HIV infection, treatment with antiretroviral therapy is necessary, but caution should be taken as life-threatening flares of MCD have been reported as a manifestation of immune reconstitution. Splenectomy can be useful in establishing the diagnosis and can induce clinical remissions, however these are short-lived and relapse typically occurs within a few months. Systemic therapy is the mainstay of treatment for patients with MCD and ranges from aggressive remission-induction chemotherapy regimens [CHOP (cyclophosphamide-doxorubicin-vincristine-prednisone); ABV (doxorubicin-bleomycin-vincristine)], single agent maintenance chemotherapy (oral etoposide, cyclophosphamide, vinblastine), immunomodulatory agents (thalidomide, interferon- $\alpha$ ), and monoclonal antibodies against the IL-6 receptor (atlizumab) and CD-20 (rituximab).<sup>171</sup>

Among all of these treatments, rituximab has shown the most promise in inducing durable remissions. In a prospective study of 24 individuals with chemotherapy-dependent HIV-associated MCD, rituximab was associated with sustained remission off treatment at day 60 (the primary end point) in 22 patients (92%).<sup>66</sup> More recently, the efficacy and safety of 4 weekly infusions of rituximab in 21 consecutive patients with previously untreated plasmablastic HIV-associated MCD has been investigated.<sup>172</sup> All but one patient achieved clinical remission of symptoms, hematological and serum chemistry normalization, and 70% achieved a radiological response. In 3 patients who relapsed, retreatment with rituximab was successful.<sup>173</sup> The main adverse event seen in these patients is reactivation of KS, which is intriguing and may be due to a rapid B-cell depletion that is observed during rituximab therapy, or an IRIS to hitherto latent antigens. Rituximab therapy in this study was shown to be associated with a decline in KSHV levels initially and at the successful treatment of relapse.

Given the lytic nature of KSHV in MCD, antiviral therapy is also a consideration. A recent randomized controlled trial demonstrated the efficacy of valganciclovir in reducing KSHV replication in individuals with KSHV infection but without evidence of KS, PEL, or MCD. In patients with MCD, ganciclovir, and valganciclovir have been independently shown to induce remissions alone or in combination with other agents.<sup>174</sup>

### Conclusion

In the 1960s, the then surgeon general of the United States announced that infectious diseases would no longer be a problem. This followed the eradication of both smallpox and polio. Since the 1980s, approximately 22 million have died of AIDS often as a result of ensuing cancers which can in some ways be regarded as opportunistic infections themselves. The peak of the AIDS epidemic in the USA occurred in 1993, and by 1995 there was a decline in the incidence of new patients due to the widespread use of HAART which in resource-rich regions resulted in a 73% decrease in the development of AIDS among HIV-infected people, and an equally remarkable 75% decline in mortality among patients with AIDS. Nonetheless, the prevalence of HIV continues to increase, driven by a stable number of new infections each year and longer survival of those infected.

HAART has also been associated with dramatic decreases in the incidence of Kaposi sarcoma, and to a lesser extent, AIDS-related lymphoma. It is now clear that effective control of the underlying HIV and its related immunosuppression prevents development of these cancers. However, the vast majority of HIV-infected individuals do not have access to HAART because of financial and social circumstances. We are thus left with the stark reality that malignant disease may be preventable but only in resource-rich areas of the world.

An understanding of the pathways that EBV, KSHV, and HPV utilize to induce cellular proliferation provides us an understanding of conserved pathways in cellular evolution.

Their targeting will undoubtedly reveal new mechanisms involved in transformation and the hope is that these in turn will reveal new drug targets that will help the eradication of both HIV and cancer.

### Summary

There is a markedly increased risk of Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer during the course of infection with the human immunodeficiency virus. Therapy for these AIDS-defining illnesses first involves antiretroviral therapy to suppress HIV viremia and maintain CD4 counts. Subsequent chemotherapy is complicated by the underlying immunoparesis and options in the management of all three diseases are discussed herein. New data related to multicentric Castlemann disease represents a model for future management of rare proliferations that are observed in the setting of HIV. Improved understanding of their etiopathogenesis will hopefully delineate new therapeutic options and strategies to control viral replication and virally induced diseases including malignancy.

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# Rheumatic Manifestations of HIV and AIDS

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## 81

### Introduction

Rheumatic manifestations can develop during the course of HIV infection at any stage of the disease but are more often seen in the late stages of the disease.<sup>1,2</sup> These musculoskeletal disorders can cause a significant morbidity in patients, thereby affecting their quality of life. The first report of Reiter syndrome in AIDS was published in 1987. Since then, a variety of musculoskeletal disorders have been described in these patients. These include non-inflammatory pain syndromes, non-specific inflammation, autoimmune diseases like vasculitis, Sjogren-like syndrome called diffuse infiltrative lymphocytosis syndrome (DILS), infectious rheumatic diseases (osteomyelitis, pyomyositis, septic arthritis), and those resulting from initiation of highly active antiretroviral therapy (HAART) (osteonecrosis, osteoporosis, myopathy). Any musculoskeletal disorder present in an HIV-negative patient can occur in an HIV-infected patient. However, its clinical presentation and the course of illness may be varied. Table 81.1 enumerates the common rheumatic manifestations of HIV and AIDS.

### Clinical Features

#### DIRECTLY RELATED TO HIV INFECTION

##### Joint Disorders

##### Arthralgias

This is the most common manifestation seen in more than 40% of cases.<sup>3</sup> Knees, shoulders, and elbows are the most frequently involved joints. Arthralgias and myalgias may present during the acute seroconversion phase or may appear in advanced stages of HIV infection. Proper counseling with reassurance and use of analgesics like paracetamol form the mainstay of treatment. The pathogenesis involves release of cytokines or transient bone ischemia.<sup>4</sup> These patients presenting with only arthralgias rarely progress to inflammatory joint disease. Recently, with the increasing use of protease inhibitors (indinavir, ritonavir, saquinavir), there is a rise in the incidence of non-specific arthralgias.<sup>5</sup>

**Table 81.1:** Rheumatic Manifestations of HIV

#### Directly related to HIV infection

HIV-associated joint disorders  
HIV-associated muscle disorders  
HIV-associated vasculitis  
Diffuse infiltrative lymphocytosis syndrome  
Serologic abnormalities  
Miscellaneous conditions

#### Consequence of immunosuppression

Septic arthritis  
Osteomyelitis  
Pyomyositis  
Soft-tissue infection

#### Related to treatment with HAART

Myopathy  
Rhabdomyolysis  
Fibromyalgia  
Carpal tunnel syndrome  
Enthesitis  
Hypertrophic osteoarthropathy  
Gout  
Osteonecrosis  
Osteoporosis  
Frozen shoulder  
Dupuytren disease  
Mycobacterial and mycotic osteoarticular disease

#### Diseases going into remission

Rheumatoid arthritis  
Systemic lupus erythematosus

##### Arthritis

It is usually an oligoarthritis, predominantly involving lower limbs, acute in onset, self-limiting, non-erosive, and lasting for less than 6 weeks.<sup>6,7</sup> Its incidence varies from 30% to 35%.<sup>8–10</sup> It is most commonly seen in sub-Saharan Africa. Commonly involved joints are knees, ankles, and metatarsophalangeal joints in lower limbs and wrists, elbows, metacarpophalangeal, and interphalangeal joints in the upper limbs. There is no association with HLA-B<sub>27</sub> or any other known genetic factor. Synovial fluid cultures are sterile. There may be a direct role of HIV as shown by the presence of tubuloreticular inclusions

in synovial fluid by electron microscopy.<sup>6,7,11</sup> Radiographs of the affected joints are invariably normal. Rarely, it may show joint-space narrowing and destruction with prolonged symptoms. Treatment includes non-steroidal anti-inflammatory drugs (NSAIDs) for 6 weeks and in severe cases, low-dose glucocorticoids (prednisolone 7.5–10 mg/day for 2 weeks) may be tried. Hydroxychloroquine 200–400 mg/day and Sulfasalazine 500 mg to 2 g/day can be used if there is no response to NSAIDs and steroids.<sup>12</sup> Jaccoud arthropathy, a non-erosive deforming arthropathy reported in systemic lupus erythematosus (SLE) and chronic rheumatic fever, has also been reported in HIV-infected patients.<sup>13</sup>

### Painful Articular Syndrome

It is a self-limited syndrome of unknown etiology lasting less than 24 hours, characterized by severe bone and joint pains.<sup>6</sup> It predominantly occurs in the late stages of HIV infection. The knee is the most commonly affected joint followed by elbow and shoulder. There is absence of synovitis, and radiographs may be normal or occasionally periarticular osteopenia may be seen. It responds well to analgesics like paracetamol 500 mg tds.

## Seronegative Spondyloarthropathies

### Undifferentiated Spondyloarthropathy

HIV-infected patients most commonly suffer from undifferentiated spondyloarthropathy as described by Solomen et al.<sup>14</sup> This type of arthropathy has features like reactive arthritis or psoriatic arthritis (PsA) but does not develop full-blown features like enthesopathy or Achilles tendonitis or plantar fasciitis. It can be treated with indomethacin 75 to 150 mg/day, local intralesional steroids, and rarely require sulfasalazine 1.5 to 2 g/day.

### Reactive Arthritis, Reiter Syndrome

The pandemic of HIV infection in Africa has resulted in an increased incidence of different types of arthritis. The risk factors for these arthritides differ in Africa and the Asian countries where heterosexual transmission is a more common cause of HIV transmission than homosexual transmission or intravenous drug abuse as seen in the western world. The clinical features, diagnostic, and radiological features are similar to HLA-B<sub>27</sub>-related arthritis. The typical presentation is lower-extremity peripheral arthritis, enthesitis, dactylitis (sausage digits), Achilles tendonitis, plantar fasciitis, keratoderma blennorrhagica, circinate balanitis, and psoriaform rashes. Asymmetrical knee or ankle involvement, clinically asymptomatic sacroilitis, which may be seen radiologically, are the commonest joints affected. The triad of urethritis, arthritis, and uveitis is commonly seen as in HIV-negative patients.

The immunopathogenesis of Reiter syndrome is linked to HLA-B<sub>27</sub>.<sup>15</sup> The association of HIV and Reiter syndrome can be explained by severe immunosuppression, which predisposes to the presence of arthritogenic microorganisms. HIV patients are more prone for gastrointestinal and genitourinary infections (*Shigella*, *Entamoeba*, *Giardia*, *Chlamydia* etc). The course of

Reiter syndrome may be severe, progressive, and refractory to treatment than in HIV-negative patients.<sup>16</sup>

The mainstay of treatment of Reiter syndrome includes indomethacin 75–150 mg/day and sulfasalazine 1.5–2 g/day. Some patients respond to hydroxychloroquine 200–400 mg/day and HAART. Methotrexate and azathioprine are best avoided as they can cause severe immunosuppression; however, they can be used with careful monitoring of CD4 counts and viral load.

### Psoriatic Arthritis (PsA)

The articular disease is either sustained, aggressive, and progresses to erosions or it is characterized by mild and intermittent joint involvement. PsA may be severe in HIV-infected individuals. There is an increased prevalence of PsA in HIV patients.<sup>9,17,18</sup> The arthritis is polyarticular disease involving lower limbs mainly foot and ankle presenting as enthesopathy and dactylitis. The sacroiliac and spinal joints are also commonly affected. Frank synovitis and effusions are less frequent. Nail involvement is commonly associated with arthritis of distal interphalangeal joint.

The course of psoriatic arthropathy during HIV infection is variable but tends to progress with the decrease in the CD4 count and appears to be refractory to conventional treatment. In this regard, the presence of psoriasis can be considered as a sign of poor prognosis in HIV infection.<sup>19,20</sup> HIV infection can precipitate or worsen pre-existing psoriasis and the appearance of new psoriatic lesions is a well-recognized cutaneous manifestation of HIV. Seborrhoeic dermatitis occurs in up to 20% of patients with HIV infection and its overlap with psoriasis (so-called seborrhoeic psoriasis) is an uncommon but highly characteristic manifestation of HIV infection.<sup>21</sup>

Indomethacin is used as an anti-inflammatory agent. Phototherapy with ultraviolet A can result in control of skin rash but increases viral replication. Methotrexate, sulfasalazine, HAART, tumor necrosis factor- $\alpha$  blockers, cyclosporine, etretinate can be used with close monitoring of CD4 count and viral load.

## HIV-Associated Muscle Disorders

Muscle disease was one of the first rheumatic complications to be seen in HIV-positive patients and there is a spectrum of muscle disease associated with this infection.<sup>22</sup> Muscle involvement ranges from myalgias, fibromyalgias to disabling HIV-associated polymyositis (PM) or pyomyositis. Various HIV-associated muscle disorders are listed in Table 81.2.

**Table 81.2:** HIV-Associated Muscle Disorders

Myalgias and fibromyalgias
Polymyositis
Nemaline rod myopathy
HIV associated wasting syndrome
Treatment related myopathies
Infections like pyomyositis, Toxoplasmosis
Rhabdomyolysis
Tumor infiltrations of skeletal muscle
Inclusion body myositis



**Myalgias and Fibromyalgias**

About one-third of the HIV-positive patients complain of myalgias<sup>9</sup> and 11% complain of fibromyalgias.<sup>23</sup> They are treated with analgesics, tricyclic antidepressants, or selective serotonin reuptake inhibitors as in HIV-negative patients.

**Inflammatory Myopathies**

HIV-associated Polymyositis (PM) presents as subacute progressive proximal muscle weakness in upper and lower limbs with more predilection for lower limbs as seen in HIV-negative patients. Ocular, facial, and pharyngeal muscles are spared.<sup>24</sup> It may be seen early in HIV disease or as a part of immune reconstitution inflammatory syndrome (IRIS).<sup>22</sup> HIV-associated PM tends to respond to much lower doses of corticosteroids (0.5 mg/kg of oral prednisolone) than in patients with idiopathic PM. Refractory cases may require methotrexate, azathioprine, mycophenolate mofetil, or intravenous immunoglobulins.

**Nemaline Rod Myopathy<sup>25</sup>**

It is a diagnosis made after muscle biopsy. It is seen in congenital and acquired myopathies. The presence of atrophic type I fibers with numerous intracytoplasmic rod bodies seen on EM are the characteristic muscle biopsy features. Its presence should arouse the suspicion of HIV infection. Steroids may be helpful in some cases.<sup>26</sup>

**HIV-Associated Wasting Syndrome**

It has been associated with progressive weight loss and an active non-inflammatory myopathy. It is also called as “slim disease” in Africa.<sup>26</sup> Treatment consists of corticosteroids, anabolic steroids, human growth hormone, nutritional supplements, and cytokine antagonists.

**Treatment-Related Myopathies**

The use of nucleoside analogs for the treatment of HIV infection has been associated with myopathy. Fifteen to forty percent patients receiving zidovudine (AZT) develop increased serum concentrations of creatine phosphokinase, clinical myositis with myalgias, or weakness or both. It may be difficult to distinguish this condition clinically from HIV-associated PM. Dalakas et al<sup>25</sup> have demonstrated that muscle biopsy is helpful in differentiating AZT-related myopathy from HIV-associated PM. Numerous ragged-red fibers indicative of abnormal mitochondria with paracrystalline inclusions were found in the muscle biopsy of patients treated with AZT only. AZT-induced mitochondrial damage with cytochrome oxidase deficiency has also been reported in literature.<sup>27</sup> Stoppage of the drug can cause reversal of this myopathy within 4 to 8 weeks.

Recently, a few cases have been reported with a syndrome of hepatic steatosis, lactic acidosis, and myopathy with increased creatine phosphokinase in patients taking stavudine.<sup>28</sup> Direct mitochondrial injury is postulated as the underlying mechanism.

The muscle biopsy is suggestive of abundance of lipid droplets with associated muscle inflammation.

**Rhabdomyolysis**

It can occur in all the stages of HIV. It may be seen in primary HIV infection or it can occur with opportunistic infections of the muscles or it may be drug induced. Drugs like didanosine, lamivudine, ritonavir, indinavir, and trimethoprim-sulfamethoxazole can cause rhabdomyolysis.<sup>29</sup>

**Inclusion Body Myositis**

It is a well-recognized complication of HIV infection.<sup>30</sup> Its clinical features and treatment are similar to sporadic inclusion body myositis as seen in HIV-negative patients.

**HIV-Associated Vasculitis**

Different patterns of vasculitis have been described in patients with HIV infection. Small-vessel vasculitis presents as peripheral neuropathy (leukocytoclastic vasculitis) often misdiagnosed as drug toxicity (hypersensitivity angitis)<sup>24</sup> or as Henoch–Schönlein purpura. Medium-vessel involvement presents as polyarteritis nodosa, which is the most common type of vasculitis seen in HIV patients. Large-vessel involvement presents as giant cell arteritis (very rare), Wegener granulomatosis, and vasculitis causing aneurysm of aorta and its primary branches such as carotid, femoral, and superior mesenteric arteries. Cytomegalovirus vasculitis, Kawasaki disease, and cryoglobulinemia have also been described in HIV patients. In children, a cerebral vasculopathy with microaneurysm formation is commonly seen.<sup>31</sup> A large-vessel aneurysmal vasculitis has been exclusively reported from Africa.<sup>32,33</sup> Behcet syndrome and relapsing polychondritis have been reported in anecdotal case reports and they respond to HAART.<sup>34</sup>

Although anti-neutrophilic cytoplasmic antibodies (ANCA) have been described in HIV-seropositive patients, these antibodies do not have a role in the pathogenesis of HIV-associated vasculitis. Immunoglobulin M and complement have been demonstrated in vessel walls, which suggest immune-complex deposition as the possible pathogenetic mechanism of vasculitis in HIV.<sup>35</sup> Whether HIV itself can cause vasculitis is unclear.

Whether HIV and vasculitis have a casual association or they occur coincidentally is not yet understood. HIV-associated vasculitis is usually not life-threatening and presents as single flare rather than relapsing illness. Hepatitis B and C should be ruled out in all HIV-associated vasculitis. Corticosteroids form the mainstay of the treatment. Immunosuppressants are given for resistant cases with careful monitoring of CD4 and viral load. Intravenous immunoglobulins and plasmapheresis should be considered in advanced immunosuppression and progressive vasculitis in HIV cases. Anti-CD25 is effective for cerebral vasculitis associated with HIV infection.<sup>36</sup> There are very few reports on the efficacy of HAART in the treatment of HIV-associated vasculitis.

## Diffuse Infiltrative Lymphocytosis Syndrome (DILS)

A syndrome similar to Sjogren syndrome characterized by massive and painless parotid gland enlargement, xerostomia, extraglandular features (lymphocytic interstitial pneumonia, renal tubular acidosis, lymphocytic hepatitis, lymphocytic meningitis, facial palsy) and peripheral CD8+ lymphocytosis has been described commonly in HIV-positive patients. It can appear at any stage of HIV disease. The frequency of DILS ranges between 3% and 78% as reported in different series.<sup>37,38</sup> The diagnosis is made by the presence of HIV seropositivity by ELISA and western blot, bilateral salivary gland enlargement or xerostomia lasting for more than 6 months, salivary or lacrimal gland histology showing lymphocytic infiltration in the absence of granulomatous, or neoplastic enlargement.<sup>39</sup> Anti-nuclear antibody (ANA), SSA (anti-Ro)/SSB (anti-La), and rheumatoid factor are usually negative. Men are more commonly affected than females and extraglandular features are more commonly seen than Sjogren syndrome. Computerized tomography scan of salivary glands may be helpful in ruling out cysts or malignancy. The treatment consists of reassurance, artificial saliva (mouth spray), pilocarpine 5 to 10 mg tds, prednisolone 30 to 40mg/day, and maintenance of dental care. The glandular swelling responds well to HAART.

## Serological Manifestations

In early disease, HIV predominantly infects macrophages. There is an increased production of proinflammatory cytokines, lymphocyte proliferation, and B-cell activation to produce hypergammaglobulinemia and autoantibodies. These are ANA, anti-erythrocyte, anti-CD4 lymphocyte, anti-platelet, rheumatoid factor, anti-protein S, anti-cardiolipin, and ANCA.<sup>40</sup> Most prominent amongst these are anti-phospholipid antibodies, immunoglobulin G, and immunoglobulin M. Although these antibodies are seen commonly in HIV patients, they rarely give rise to thrombotic phenomena. ANA are seen in 10–30% of HIV patients. These antibodies are usually present in low titers. They occur in patients with advanced HIV infection, low CD4 counts, and are associated with increased mortality.<sup>41</sup> Thus, the presence of most of these antibodies, indicate B-cell activation. They are not actually involved in the pathogenetic mechanisms. The few autoantibodies that are pathogenic include anti-platelet/anti-erythrocyte, which cause immune thrombocytopenic purpura and hemolytic anemia in a minority of patients.

## Miscellaneous Rheumatic Conditions

Osteonecrosis, hypertrophic osteoarthropathy, Behcet syndrome, Sweet syndrome, adult onset Still's disease, heterotropic ossificans, and primary pulmonary hypertension have been described in HIV-infected patients.<sup>42</sup> Hypertrophic pulmonary osteoarthropathy is seen in patients with *Pneumocystis jiroveci* pneumonia and resolves with treatment of pneumonia.<sup>43</sup> Primary pulmonary hypertension is more commonly seen in younger patients with

AIDS. The responses to vasodilator agents like calcium channel blockers, sildenafil, intravenous and inhaled prostanoids, and endothelin antagonists are promising in the treatment of primary pulmonary hypertension.

## CONSEQUENCE OF IMMUNOSUPPRESSION

Musculoskeletal infections can occur as an effect of immunosuppression. The incidence of these infections has been reported to be less than 1% in a large series.<sup>24,44–46</sup> The various musculoskeletal infections are septic arthritis, soft-tissue infections like cellulitis and pyomyositis, osteomyelitis, and rarely septic bursitis.

## Septic Arthritis

It may be the first manifestation of AIDS when CD4 cell count falls to less than 100/ $\mu\text{L}$ .<sup>3</sup> Acutely swollen; painful; tender, red, hot joint, accompanied by systemic symptoms of bacteremia is the typical presentation. *Staphylococcus aureus*, *Stenotrophomonas maltophilia*, *Prototheca wickerhamii*, and *Candida albicans* are common organisms causing septic arthritis.<sup>47</sup> The important risk factors for septic arthritis are IV drug abuse, previous intra-articular injection or synovial fluid aspiration from the joint, psoriasis or pustular skin infection around the joints. Intracellular organisms like *Mycobacterium tuberculosis*, *M. kansasii* and *M. avium*; fungi like *Candida albicans*, Cryptosporidia, Histoplasma and Pseudomonas are the common pathogens in IV drug abusers. Gonococci is the organism common in patients who have received intra-articular injections or synovial fluid has been aspirated. With impaired immune response of the host, the signs of inflammation may be minimal. Hence, it is important to examine the synovial fluid of every HIV-positive patient having joint effusion.

In a study of 43 cases of hemophiliacs with Patients of hemophilia with AIDS can develop septic arthritis. In a study reported by Barzilia et al., the clinical features of septic arthritis in hemophiliacs with AIDS resemble those of hemarthrosis. In both these conditions, there is high ESR, fever and the affected joint is warm, tender and swollen. However, in these patients there is absence of peripheral leukocytosis and the CD4 count is variable. Treatment with systemic antibiotics is sufficient and arthrotomy and open drainage is rarely required.<sup>48–51</sup>

## Soft-Tissue Infections

Although rare, these range from cellulitis, soft-tissue abscesses to pyomyositis. They occur when CD4 cell count falls to less than 200 cells/ $\mu\text{L}$ .<sup>3</sup> Intravascular indwelling catheters, trauma, and extra-articular infection are the predisposing factors.<sup>52</sup> The clinical features and treatment outcome are almost similar to that in HIV-negative patients.

## Tropical Pyomyositis

It is an acute bacterial infection of skeletal muscles characterized by rapid formation of abscesses. Acute onset unilateral thigh pain

with swelling, erythema, and woody induration are the typical clinical features. It can simulate septic arthritis of knee and hip as the thigh muscles are commonly involved. Ultrasonography, computerized tomography, or magnetic resonance imaging of the affected part with aspiration of pus confirms the diagnosis. Occurrence of tropical pyomyositis is a criterion for classifying HIV-infected patients in WHO stage III. The most common organism is *Staphylococcus aureus*<sup>53</sup> followed by *Salmonella*.<sup>54</sup> Other organisms are *Streptococcus pneumoniae*, *Citrobacter freundii*, and *Microsporidia*.

## Osteomyelitis

Clinical features are similar to septic arthritis. But it is usually associated with a poor prognosis and requires more prolonged treatment with antibiotics. Bacillary angiomatosis osteomyelitis is a disease seen only in HIV-positive patients.<sup>4</sup>

## Tuberculosis

Tuberculosis is one of the most virulent opportunistic infections and it appears fairly early in HIV disease. HIV specifically eliminates macrophages and CD4 cell count that provide immunity against tuberculosis. Musculoskeletal manifestations may occur in 2% of cases. These are spondylitis, osteomyelitis/mono-oligo-polyarthritis,<sup>55</sup> Poncet disease, and tuberculous dactylitis. Infectious arthritis and tenosynovitis are caused by *M. kansasii*. *M. xenopi* causes spondylodiscitis in AIDS patients. Also, the drugs used for the treatment of tuberculosis can give rise to rheumatic conditions. For example, rifabutin or clarithromycin can precipitate uveitis, fluoroquinolones can cause tendonitis, and pyrazinamide can lead to hyperuricemia and gout.

## RHEUMATIC MANIFESTATIONS OCCURRING AFTER HAART

A dramatic change has taken place in the treatment of HIV infection after the introduction of HAART. Although HAART has extended life expectancy in HIV-infected patients, it is not free from complications. These complications include both metabolic and inflammatory disorders, which may present as rheumatic manifestations.

## Metabolic Complications

### Osteonecrosis

Four percent of HIV-positive patients may have osteonecrosis.<sup>56</sup> It is one of the late complications of HIV. Osteonecrosis or avascular necrosis of the bone occurs due to impairment of blood supply to bone. Tissue necrosis takes place in the subchondral bone, which may ultimately lead to compression and deformity of the articular surface. Various studies have demonstrated significant associations with the use of glucocorticoids, lipid-lowering agents, anabolic steroid use, protease inhibitors-based HAART treatment, alcohol abuse,

and hypercoagulability.<sup>57</sup> The most common presenting symptom is pain on weight-bearing. Some patients may be asymptomatic and diagnosis is made by radiological studies.

### Osteoporosis

Osteopenia and osteoporosis occur more than 3 times as commonly in HIV-infected patients regardless of HAART<sup>58</sup> and can result in pathologic fractures. Risk factors for the development of osteopenia are use of protease inhibitors, longer duration of HIV infection, high viral load, high lactate levels, low bicarbonate levels, increased alkaline phosphatase levels, and lower body weight before HAART.<sup>59</sup> The role of HAART as a contributing factor in the development of osteopenia or osteoporosis is controversial.<sup>60</sup> Some authors have attributed abnormal bone metabolism to the HIV infection itself.<sup>61</sup> Bisphosphonates, calcium, and vitamin D are used to preserve bone density.

### Gout

Abnormalities in urate metabolism have been described in HIV-positive patients. Asymptomatic hyperuricemia can occur in 41% and symptomatic hypouricemia in 5%. Acute gout attacks have also been described. Asymptomatic hyperuricemia and gout are commonly seen in patients who receive ritonavir as a boosted protease inhibitor and who also have lipodystrophy.<sup>62</sup>

## Autoimmune/Inflammatory/Infectious Complications

The introduction of HAART in a patient with HIV infection is followed by suppression of HIV replication and a rise in peripheral CD4 lymphocyte counts and a varying degree of immune restoration. This leads to an inflammatory reaction to occult pathogens in 20–25% of patients with advanced disease known as IRIS or immune restoration disease.<sup>63</sup> In a recent review of 32 cases, sarcoidosis, autoimmune thyroid disease, Reiter syndrome, and various connective tissue diseases like RA, SLE, and PM have been reported.<sup>64</sup> The mean time from the introduction of HAART to the appearance of clinical autoimmune/inflammatory disease is approximately 9 months and most cases are mild or self-limiting and resolve with little or no therapy.<sup>65</sup>

Mycobacterial and mycotic osteoarticular infection, neoplasia, rhabdomyolysis, septic arthritis, cellulitis, osteomyelitis, discitis, pyomyositis, fibromyalgia, seronegative symmetrical polyarthritis, carpal tunnel syndrome, enthesitis, multifocal bone non-Hodgkin lymphoma, and hypertrophic osteoarthropathy have been reported in anecdotal case reports as rheumatological manifestations after starting HAART.

Indinavir-associated monoarthritis,<sup>66</sup> frozen shoulder, temporomandibular joint dysfunction, and Dupuytren disease<sup>5</sup> have been reported in literature. With the advent of HAART, there is an increase in life expectancy, but new rheumatic complications such as osteonecrosis, osteoporosis, gout, mycobacterial, and mycotic osteoarticular infections may become more prevalent.



## AUTOIMMUNE DISEASES GOING INTO REMISSION OR LESS COMMONLY SEEN IN HIV

### Systemic Lupus Erythematosus

HIV patients can share many clinical, laboratory, and serological findings as seen in SLE. Concomitant HIV infection and SLE have been reported although rare.<sup>67</sup> Lupus-like syndrome has been described in HIV. The significance of presence of different types of autoantibodies in HIV-infected patients is still uncertain and may reflect polyclonal B-cell activation as discussed earlier. Autoantibodies like ANA, anti-double-stranded DNA (anti-dsDNA), anti-Smith antibody, anti-parietal cell, anti-glomeruli, anti-thyroid, and ANCA<sup>41</sup> also occur frequently in both diseases. Although, theoretically, both these diseases would be mutually exclusive, SLE should be considered in HIV-positive patients with rheumatologic complaints.<sup>8</sup>

HIV infection can result in clinical improvement of the disease activity in lupus patients and disappearance of autoantibodies when the CD4 cell counts are low.<sup>67</sup> A clinical improvement can also occur when CD4 cell counts are normal. Treatment with ART leads to restoration of the immune system which can flare SLE.<sup>67</sup> Conversely, SLE treatment with immunosuppressive drugs can lead to HIV replication and rapid progression in the clinical course of HIV.<sup>68</sup> Treatment of the two conditions is decided on the basis of individual patient with careful monitoring of the CD4 cell count, viral load, autoantibodies, ESR, C-reactive protein, complement levels, and the clinical response to treatment.

### Rheumatoid Arthritis

Patients with RA who go into remission after HIV infection with clinical immunosuppression have been reported.<sup>69,70</sup> CD4 cell count depletion is the postulated mechanism. RA patients having active disease and radiologic progression despite an immunosuppressive state of HIV infection, have also been described.<sup>71,72</sup>

### Antiphospholipid Antibody Syndrome

False-positive syphilis tests and the lupus anticoagulant have been reported in 40–50% of HIV-positive patients in advanced stages.<sup>73</sup> High titers of anticardiolipin antibodies have been detected in a significant proportion of HIV-positive patients who are clinically asymptomatic. The immunoglobulin G anticardiolipin antibodies isotype has been found in 85–95% of patients with advanced HIV infection.<sup>74</sup> One study has reported high frequency of anti-phospholipid antibodies particularly for isotype IgA anti- $\beta_2$  glycoprotein.<sup>75</sup> However, there was no association with clinical manifestations of antiphospholipid antibody syndrome.

### Conclusion

Thus, HIV-infected patients can have similar rheumatologic conditions as seen in HIV-negative patients. Management of these conditions can pose difficulties to the treating physician/

rheumatologist as the immunosuppressive agents can rapidly cause full-blown AIDS in HIV-infected patients. These drugs are to be used cautiously with careful monitoring of the viral load and CD4 cell counts. With the availability of HAART, some inflammatory conditions undergo remission but IRIS, infections, and metabolic complications of HAART manifesting as rheumatological disorders should be kept in mind due to their rising incidence.

#### Summary

- Rheumatic manifestations can develop during the course of HIV infection at any stage of the disease but are more often seen in the late stages of the disease. These range from non-inflammatory pain syndromes, non-specific inflammation, autoimmune diseases like vasculitis, Sjogren syndrome called diffuse infiltrative lymphocytosis syndrome (DILS) to infectious rheumatic diseases (osteomyelitis, pyomyositis, septic arthritis), and those resulting from initiation of highly active antiretroviral therapy (HAART) (osteonecrosis, osteoporosis, myopathy).
- Several serological markers like ANA, rheumatoid factor, antiphospholipid antibodies may be found in the serum of HIV-positive patients in the absence of the clinical features.
- With the advent of HAART, there is an increase in life expectancy; but new rheumatic complications such as osteonecrosis, osteoporosis, gout, mycobacterial, and mycotic osteoarticular infections may become more prevalent.
- Management of the rheumatological conditions can pose difficulties to the treating physician/rheumatologist as the immunosuppressive agents can rapidly cause full-blown AIDS in HIV-infected patients.

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# Cardiac Involvement in HIV Infection/AIDS

Yash Paul Sharma • Rakesh Raman Patyar

# 82

## Introduction

Acquired immune deficiency syndrome (AIDS) is a global health crisis affecting approximately 33.3 million people worldwide. In 2009, AVERT (formerly known as the AIDS Education and Research Trust) estimated approximately 1.8 million annual deaths due to AIDS and 2.6 million new HIV infections per year. AIDS progressively reduces the effectiveness of the immune system thereby making patients more susceptible to opportunistic infections and tumors. Advances in highly active antiretroviral therapy (HAART) have reduced both the mortality and the morbidity of HIV infection. Although HIV infection has been associated with cardiac manifestations since pre-HAART era, reports of increased incidence of cardiovascular manifestations after the introduction of HAART and also due to increased life span have raised serious concerns. Various studies have indicated that HAART is associated with an increase in both peripheral and coronary arterial diseases. Moreover, the association of HIV with cardiac manifestations has become so evident and common that it is being considered as a potential risk factor for coronary artery disease. However, the risk of cardiac involvement is quite variable as it depends on a variety of factors like the stage of HIV disease, the immune-status of the patient, type of drugs being used to treat the disease, and the presence of opportunistic infections or neoplasms. The cardiac manifestations associated with HIV include coronary artery disease, dilated cardiomyopathy (DCM), pericardial effusion, pulmonary hypertension leading to heart failure, conduction system abnormalities, and neoplastic infiltration. A variety of mechanisms have been implicated in this association. But the principal underlying causes are direct invasion by HIV as well as the occurrence of opportunistic infections.

Here we will discuss the issues regarding the principal HIV-associated cardiovascular manifestations, their potential causes/mechanisms (Table 82.1), prevalence, pathogenesis, and management. Due to lack of proper guidelines, there is a growing need for generating awareness so that HIV-associated cardiovascular diseases can be diagnosed, prevented, or treated early in the course.

**Table 82.1:** Principal Cardiac Diseases in HIV-infected/AIDS Patients Along with Their Potential Causes

Type	Potential causes
<b>Myocardial diseases</b> HIV-associated dilated cardiomyopathy	<b>Infection leading to myocarditis</b> HIV, Coxsackie virus group B, Epstein–Barr virus, cytomegalovirus, adenovirus <b>Drug-related cardiotoxicity</b> Zidovudine and phosphorylated azidothymidine <b>Autoimmunity</b> Anti- $\alpha$ -myosin antibodies <b>Nutritional deficiencies</b> Selenium, carnitine, vitamin B <sub>1</sub> and B <sub>12</sub> <b>Endocrine</b> Growth hormone and thyroid hormone
<b>Endocardial diseases</b> Infective endocarditis	<b>Bacteria</b> <i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i> , and <i>Haemophilus influenzae</i> <b>Fungus</b> <i>Candida albicans</i> , <i>Aspergillus fumigatus</i> , and <i>Cryptococcus neoformans</i> Rheumatic fever, hypercoagulable states, and trauma (e.g., catheters)
Nonbacterial thrombotic endocarditis	
<b>Pericardial diseases</b> Pericardial effusion	HIV itself, opportunistic infections Malignancies (Kaposi sarcoma, non-Hodgkin lymphoma)
Pericarditis	HIV itself, opportunistic infections
<b>Vascular diseases</b> Atherosclerosis	<b>Dysfunctional endothelial cells</b> Potentiate tissue injury, inflammation, and remodeling <b>Virus infected monocyte macrophages</b> Alter leukocyte adhesion or arteritis Recurrent bronchopulmonary infections, pulmonary arteritis Microvascular pulmonary emboli due to thrombus or drug injection Mediator release from endothelium
Pulmonary hypertension	

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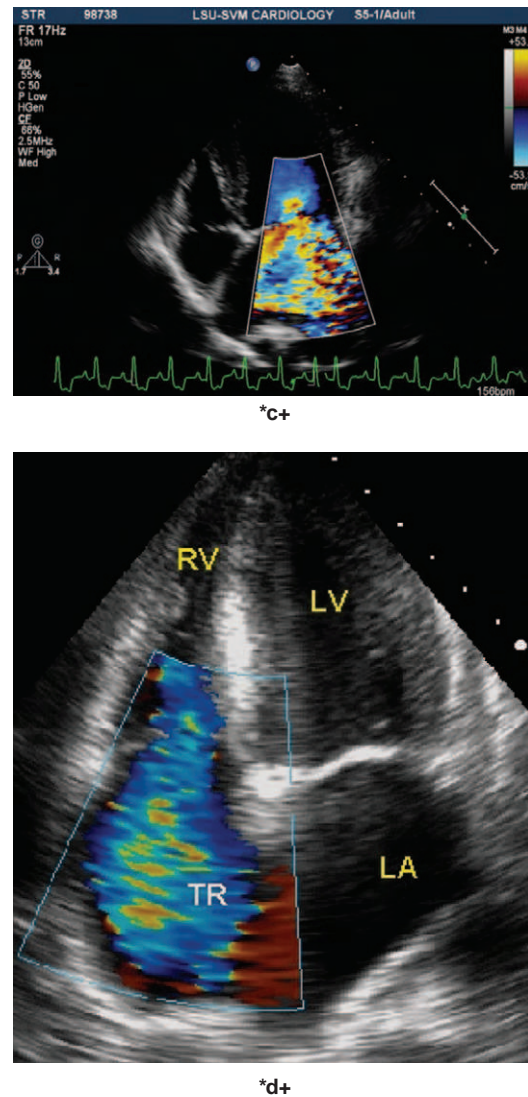
Type	Potential causes
<b>Coronary artery disease</b>	<b>Endothelial cells</b> Alter the procoagulant, anticoagulant, and fibrinolytic pathways Unusual proliferation of smooth muscle cells, mixed with abundant elastic fibers Side-effects of combined antiretroviral therapy Coronary arteriopathy
<b>Cardiovascular malignancies</b>	Kaposi sarcoma Non-Hodgkin lymphoma
<b>Cardiac arrhythmias</b>	
Prolonged QTc interval	<b>Protease inhibitors</b> Block the human ether-a-go-go related gene channel
Torsades de Pointes	<b>Antiretroviral drugs such as pentamidine</b> Hypomagnesemia

## HIV-Associated Cardiovascular Manifestations

### MYOCARDIAL DISEASE

HIV disease is considered as a potential risk factor of dilated cardiomyopathy (DCM). DCM had been described in up to 30–40% of patients with AIDS in clinicopathological studies performed in the pre-HAART period.<sup>1</sup> The median survival was found to be 101 days in patients with left ventricular dysfunction compared with 472 days in HIV infected patients with a normal echocardiogram at the same stage of infection.<sup>2</sup> DCM occurs late in the course of HIV infection and is caused by a complex and multifactorial mechanism. The most important cause is myocarditis which itself is secondary to HIV or other infectious agents. HIV-1 virions infect myocardial cells thereby leading to progressive cardiac myocyte dysfunction. Another major cause for the development of HIV-associated DCM is the cardiotoxicity of drugs used in HIV infection, e.g., zidovudine and phosphorylated azidothymidine. As increased levels of anti- $\alpha$ -myosin antibodies have been reported in patients with HIV-associated cardiomyopathy cardiac autoimmunity too has been implicated in its pathogenesis. Nutritional deficiencies (selenium, carnitine, vitamin B<sub>1</sub> and B<sub>12</sub>) which are very common in HIV infection are also held responsible for development of DCM as they contribute in inducing ventricular dysfunction independently of HAART regimens. Similarly, deficiencies of trace elements have been associated directly or indirectly with cardiomyopathy. Altered levels of growth and thyroid hormone also have been associated with left ventricular dysfunction. Gross pathologic features of HIV-associated DCM include endocardial fibrosis and mural thrombus, while histological features involve myocyte hypertrophy and degeneration, with increased interstitial and endocardial fibrillar collagen often associated with evidence of previous myocarditis. DCM may result in secondary mitral and tricuspid regurgitation also (Fig. 82.1 a & b).

The most sensitive and specific method for the evaluation of DCM is echocardiography. In a prospective study of 952 asymptomatic HIV positive patients, an echocardiographic



**Fig. 82.1 a & b:** 2-D color Doppler showing mitral and tricuspid regurgitation, respectively, in HIV cardiomyopathy. *Courtesy: Dr. Arun Gopi; PGIMER, Chandigarh.*

diagnosis of DCM was made in 76 (8%) patients with a mean annual incidence of 15.9/1000 patients. All patients with echocardiographic abnormalities underwent endomyocardial biopsy. Myocarditis was present in 63 (83%) of the patients with DCM and 36 (57%) of these had a positive hybridization signal for HIV. Coinfection with coxsackie virus, cytomegalovirus (CMV), and Epstein–Barr virus (EBV) was also noted in many cases.<sup>3</sup> In a recent study, echocardiographic findings were identified in 22 of 52 HIV-positive patients (42.3%). Eighteen patients (34.6%) were having decrease in fractional shortening, 10 patients (19.2%) had left ventricular diastolic dysfunction, 8 patients (15.4%) had global hypokinesia and pericardial effusion was present in 6 patients (11.5%). Nineteen out of 22 patients having CD4 cell count <100 cells/ $\mu$ L had echocardiographic abnormalities. Patients with opportunistic infections had more frequent echocardiographic abnormalities than those without

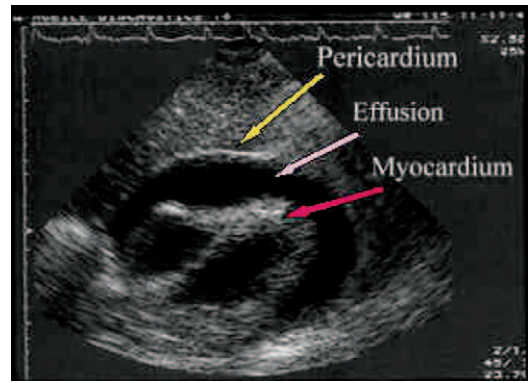
opportunistic infections ( $P < 0.001$  for TB, candidiasis and various pneumonias).<sup>4</sup> Echocardiography is helpful in detecting diastolic dysfunction in early disease. Computer tomography (CT) and magnetic resonance tomography (MRI) may help to clarify the etiology, especially in cases secondary to neoplastic infiltrations. However, the need for routine endomyocardial biopsy is controversial. ACE inhibitors and beta-blockers are recommended, but may be poorly tolerated because of low systemic vascular resistance due to associated diarrheal disease, infection, or dehydration. There is enhanced sensitivity to digoxin.

### ENDOCARDIAL DISEASE

HIV-associated endocardial diseases include nonbacterial thrombotic endocarditis as well as infective endocarditis. Vegetations form on the tricuspid and pulmonary valves with resultant pulmonary embolism and septic pulmonary infarction. Nonbacterial thrombotic endocarditis, also known as marantic endocarditis, occurs in 3–5% of AIDS patients with mostly having HIV related wasting syndrome. Here left sided valves are frequently affected, and the vegetations are mostly friable.<sup>5</sup> The prevalence of infective endocarditis varies from 6.3% to 34% in the HIV-infected patients who use intravenous drugs independent of HAART regimens.<sup>5</sup> In this case, right-sided valves are predominantly affected. *Staphylococcus aureus* (>75% of the cases) is the most common pathogen, followed by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Candida albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans*. Since the introduction of HAART, marantic endocarditis is less frequent and has rarely been a cause of death in HIV-infected patients. Clinical presentation, diagnosis, and management of infective endocarditis in HIV-patients are similar to that seen in the general population. Medical therapy is successful in >70% of cases and surgery also has good outcome.

### PERICARDIAL DISEASE

The prevalence of pericardial effusion in asymptomatic HIV-positive patients is estimated at 11%.<sup>6</sup> There is no apparent correlation between clinical stages of HIV infection and severity of pericardial involvement. Pericardial effusions in HIV diseases may be related to HIV itself, opportunistic infections, or malignancies (Kaposi sarcoma, non-Hodgkin lymphoma), but most often a clear etiology is not found (Fig. 82.2). The pericarditis is usually nonspecific in origin and can occur with or without effusion. Low pressure tamponade may be encountered in patients with AIDS who are severely dehydrated and cachectic with low resting right ventricular filling pressures. Echocardiography is considered as the standard method for diagnosis and control of pericardial diseases. But in case a neoplasm or an increase in the cardiac lipid tissue is suspected, diagnosis should be performed by CT/MRI. Small asymptomatic effusions do not require diagnostic evaluation and spontaneously resolve in up to 42% of the patients. However, symptomatic patients may require pericardial puncture. Pericardiectomy may be considered as an option for palliative care.



**Fig. 82.2:** 2-D color Doppler showing HIV-associated pericardial effusion. Courtesy: Dr. Arun Gopi; PGIMER, Chandigarh.

### CARDIOVASCULAR MALIGNANCIES

Two types of malignancies affect the heart in patients infected with HIV, namely, Kaposi sarcoma and malignant lymphoma, of which former is more common. Kaposi sarcoma is a low grade neoplasm arising from mesenchymal or endothelial cells and occurs in approximately 30% of the patients with AIDS, mostly male homosexuals. It may cause visceral or parietal pericardial lesions and, less frequently, myocardial lesions. Cardiac Kaposi sarcoma is not associated with clinical cardiac dysfunction, morbidity, or mortality. It is usually occult and rarely diagnosed during life. Primary cardiac malignancy associated with HIV infection is generally due to cardiac lymphoma. Non-Hodgkin lymphoma is 25 to 60 times more common in HIV-infected individuals. Lymphomatous infiltration may be diffuse or may result in discrete isolated lesions, which are usually derived from the Burkitt or immunoblastic type B cells. Clinical manifestations of cardiac lymphoma include cardiomegaly, pericardial effusions, congestive heart failure, arrhythmias, and progressive heart block. Sudden death is rare. The prognosis is generally poor and the optimal approach to treatment has yet to be determined, though clinical remission has been obtained with combination chemotherapy.

### VASCULAR DISEASE

In HIV infection, dysfunctional endothelial cells potentiate tissue injury, inflammation, and remodeling, which further accelerates the development of cardiovascular diseases.<sup>7</sup> In HIV infected patients, because of atherogenesis stimulated by virus infected monocyte macrophages, there may be acceleration of vascular disease, possibly as a result of altered leukocyte adhesion or arteritis. The reported arterial lesions include arteriopathy with or without aneurysm formation, fibrocalcific lesions, and endothelial proliferation in association with Kaposi sarcoma. Primary pulmonary hypertension has been reported in disproportionate number of HIV infected individuals and is estimated to occur in 0.5% of the hospitalized patients with AIDS.<sup>8</sup> The pathogenesis of primary pulmonary hypertension in HIV infection is multifactorial and quite uncertain.



Isolated right ventricular hypertension with or without right ventricular dilation is generally related to pulmonary diseases that increase pulmonary vascular resistance, such as recurrent bronchopulmonary infections. The clinical symptoms and the outcome of patients with right ventricular dysfunction are related to the degree of pulmonary hypertension, varying from a mild asymptomatic condition to severe cardiac impairment and even death. The effect of HAART on pulmonary hypertension is not known; however, a recent study has reported that pulmonary artery pressure increased in untreated patients but decreased in HAART-treated patients. Similarly the effect of epoprostenol therapy on the prognosis of HIV-infected patients with pulmonary hypertension is not clear. However, it is generally used in seriously ill patients because of the need for continuous intravenous infusion with an associated risk of infection. The oral endothelin receptor antagonist, bosentan, has been reported to improve hemodynamic measurements in HIV patients.

### CORONARY ARTERY DISEASE AND HYPERTENSION

Coronary artery disease (CAD) is observed with increasing frequency among HIV-infected patients receiving HAART. Patients with pre-existing cardiovascular risk factors have a higher risk of developing acute coronary syndrome and stroke. However, data on the incidence of CAD among HIV-infected subjects receiving HAART is lacking. Presently, this information is limited to case reports. HIV-infected patients are at higher risk of developing hypertension at a younger age than the general population.<sup>9</sup> HIV-associated CAD is characterized by unusual proliferation of smooth muscle cells, mixed with abundant elastic fibers, resulting in endoluminal protrusions. Other factors responsible for CAD are endothelial cells and the side-effects of combined antiretroviral therapy. Endothelial cells act by altering the procoagulant, anticoagulant, and fibrinolytic pathways while altered adhesion of HIV-infected monocytes-macrophages and HIV-associated angiitis lead to coronary arteriopathy. Management of HIV-associated CAD employs changes in lifestyle, cessation of tobacco use, and treatment with atherogenic lipid profiles with dietary and pharmacologic interventions. HAART has been found beneficial too.

### METABOLIC SYNDROMES

HIV has been associated with the abnormalities of lipid metabolism, such as hypertriglyceridemia and low levels of high density lipoproteins since the pre-HAART era. However, after introduction of HAART, high levels of low-density lipoprotein and total cholesterol were reported. Hypertriglyceridemia can be treated with a fibrate, and a statin can be given for concurrent hypercholesterolemia. Similarly, the incidence and prevalence of diabetes mellitus has increased since the introduction of HAART. Furthermore, there is impaired glucose phosphorylation and transport in skeletal muscle in patients infected with HIV, with lipodystrophy as a mechanism of insulin resistance. A relatively

low dosage of metformin was reported to reduce insulin resistance and related cardiovascular risk parameters in patients infected with HIV who had lipodystrophy.

### CARDIAC ARRHYTHMIAS

HIV-associated cardiac arrhythmias may depend on medication. Prolonged QTc intervals and consequential Torsades de Pointes too have been associated with HIV infection. The underlying cause of this is yet unknown. Antiretroviral drugs such as pentamidine may cause hypomagnesemia and promote Torsades de Pointes, while protease inhibitors (PIs) block the human ether-a-go-go related gene (hERG) channel and prolong QT intervals.<sup>10</sup> Management employs initiation or change of such medications after controlled daily monitoring by ECG. Arrhythmias can be treated by electrolytes and glucose, if necessary. To terminate Torsades de Pointes tachycardia, magnesium may be used.

### Toxicity due to Antiretroviral and Other Medications

There are three classes of antiretroviral drugs presently being used for people with HIV infection: nucleoside reverse transcriptase inhibitors (NRTIs), non nucleoside reverse transcriptase inhibitors (NNRTIs), and PIs—given in various combinations. Drug-induced DCM secondary to mitochondrial toxicity has been associated with zidovudine use. However, from a clinical point of view, in a study of selected HIV infected children, zidovudine neither worsened nor ameliorated cardiac functions in patients with cardiomyopathy.<sup>11</sup> Recently, a study investigated the effect of antiretroviral therapy on carotid intima-media thickness in HIV-infected patients. The study concluded that HIV-infected patients treated with PIs show earlier vascular involvement as compared to those treated with NNRTIs, and healthy subjects with similar distribution of cardiovascular risk factors. However, during the 2-year follow-up in HIV-infected patients treated with PIs, no significant differences were observed.<sup>12</sup> Hyperlipidemia, hyperglycemia, hyperinsulinemia, and lipodystrophy are frequent adverse effects of potent antiretroviral combination therapies, particularly involving PIs, thus causing the complex clinical constellation termed lipodystrophy syndrome, consisting of abnormal fat redistribution and various metabolic alterations and ultimately accelerated atherosclerosis.

### TOXICITY DUE TO OTHER MEDICATIONS

Drugs used for HIV related diseases may also have adverse cardiac effects. Erythromycin, trimethoprim, and sulfamethoxazole may cause orthostatic hypotension. Antifungals can result in hypertension, arrhythmias, and hypokalemia. Pentamidine causes arrhythmias especially Torsades de Pointes (through QTc prolongation). Arrhythmias may be precipitated by the concomitant use of drugs that share the CY3PA metabolic pathway and clinicians should be aware of this potentially dangerous interaction.

## Cardiac Involvement in Children

The rate of vertical transmission has substantially decreased in the recent years owing to administration of antiretroviral therapy during pregnancy and delivery. Most pediatric patients with HIV are infected in the perinatal period. With the use of early screening echocardiography, rates of congenital cardiovascular malformations in both the HIV infected and HIV uninfected children were similar.<sup>13</sup> Rarely encountered cardiovascular manifestations of HIV infection in children include increased left ventricular mass with systolic dysfunction, myocarditis, vascular disease, aortic root dilatation, pericardial effusion, tumors, and minor ECG abnormalities.

## Conclusion

Cardiovascular diseases have been associated with HIV-infection both before and after the introduction of HAART. As the association of cardiac manifestations with AIDS is becoming evident, there is a need for thorough cardiological screening of such patients especially for those receiving HAART regimens and having other known underlying cardiovascular risk factors. Risk factors for cardiovascular manifestations should be aggressively modified/handled along with treatment of malnutrition, anemia, and wasting in HIV infected/AIDS patients for their better survival.

### Summary

AIDS is a global health crisis afflicting vital organs, including the cardiovascular system. The HIV infection has been associated with neurologic, pulmonary, and cardiac manifestations since pre-HAART era. However, the association of HIV with cardiac manifestations has become so evident after the introduction of HAART regimens that it is now being considered as a potential risk factor for coronary artery disease. Various other cardiac manifestations associated with HIV include dilated cardiomyopathy, pericardial effusion, and pulmonary hypertension leading to heart failure, conduction system abnormalities and neoplastic infiltration. Therefore, thorough cardiological screening of patients, especially for those receiving HAART regimens and having other known underlying cardiovascular risk factors, is being suggested as a critical preventive measure.

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## Introduction

Acquired immunodeficiency syndrome (AIDS) was first described in 1981 and within 3 years the causative virus which is currently known as human immunodeficiency virus (HIV) was identified.<sup>1,2</sup> Several studies of ocular involvement in HIV/AIDS have been published from different parts of the world since the first description of ocular lesions in HIV-infected patients in 1982.<sup>3–7</sup> The first report of ocular manifestation of AIDS from India was published from Sankara Nethralaya, Chennai in 1995.<sup>8</sup> Since then two large series and a few other reports from different parts of India have been published.<sup>9–11</sup>

## Ocular Diseases in HIV Infection

Ocular diseases in HIV infection are varied and affect almost all structures of the eye. They manifest clinically in up to two-thirds of patients with AIDS at some point in their life time. However, at autopsy, 95% of AIDS patients have ocular lesions. Patients can have ophthalmic complaints during the early phase of HIV infection, and the ophthalmic manifestations of the disease can help the clinician suspect an underlying HIV infection. Ocular lesions can be classified on the basis of the involvement of various ocular structures (Table 83.1).<sup>12</sup> The frequencies of various ophthalmic manifestations in AIDS patients and their clinical presentations are shown in Table 83.2.

### ADNEXAL AND ANTERIOR SEGMENT LESIONS IN HIV INFECTION

Human immunodeficiency virus infection commonly affects the ocular adnexa. Anterior segment involvement may be the first clinical manifestation of HIV disease and it occurs in up to 50% of the patients.<sup>13</sup> The common conditions are described.

#### Herpes Zoster Ophthalmicus

Herpes zoster ophthalmicus (HZO) is caused by the varicella zoster virus and involves the ophthalmic distribution of the trigeminal nerve. Its occurrence in a person under 50 years of

**Table 83.1:** Ocular Lesions in Patients with HIV/AIDS

<i>A. Adnexal and anterior segment diseases</i>	
•	Herpes zoster ophthalmicus
•	Molluscum contagiosum of the eyelids
•	Lid infections
•	Conjunctival squamous cell carcinoma
•	Keratoconjunctivitis sicca
•	Infective keratitis (varicella zoster, herpes simplex, microsporidia)
•	Anterior uveitis
•	Ophthalmic Kaposi sarcoma
<i>B. Posterior segment diseases</i>	
•	Noninfectious HIV retinopathy
•	Opportunistic infections
•	Cytomegalovirus retinitis
•	Varicella zoster virus disease—acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN)
•	<i>Toxoplasma</i> retinochoroiditis
•	Mycobacterial infection
•	Fungal infections
•	<i>Pneumocystis jiroveci</i> choroidopathy
<i>C. Orbital lesions</i>	
•	Orbital cellulitis
<i>D. Neuro-ophthalmic diseases</i>	
<i>E. Neoplasms</i>	

age should arouse the suspicion of an immunosuppressive state. Its prevalence in the HIV infected population is reported to be 5–15%.<sup>14</sup> Concurrent posterior segment involvement may also occur. Acute panuveitis with hemorrhagic hypopyon associated with HZO has recently been reported as the initial presenting feature of AIDS.<sup>15</sup>

Treatment consists of intravenous acyclovir (10 mg/kg, 3 times a day for 7–10 days) followed by an oral maintenance regimen (800 mg 5 times daily). Famciclovir can be used in a dosage of 500 mg, 3 times daily. Intravenous foscarnet should be considered if the response to acyclovir or famciclovir is not satisfactory.

#### Molluscum Contagiosum

Molluscum contagiosum is a contagious disease caused by a poxvirus. It clinically presents as multiple, small, painless,



**Table 83.2:** Estimated Frequency of Ocular Manifestations of AIDS.

Lesions	Frequency
<b>1. Microangiopathy</b>	
• Conjunctival microangiopathy	75%
• HIV retinopathy	50–67%
<b>2. Opportunistic ocular infection—anterior segment</b>	
• Microsporidial keratoconjunctivitis	<1%
• Herpes zoster ophthalmicus	4%
<b>3. Opportunistic ocular infection—posterior segment</b>	
• Cytomegalovirus	20–25%
• Varicella zoster virus retinitis (ARN, PORN)	<1%
• Toxoplasma retinochoroiditis	1%
• Choroidal pneumocystosis	<1%
<b>4. Ocular neoplasms</b>	
• Eyelid Kaposi sarcoma	1–2%
• Conjunctival Kaposi sarcoma	1–2%
• Orbital lymphoma	<1%
• Neuro-ophthalmic lesions	10%

umbilicated lesions, which are larger and more numerous in HIV positive individuals.<sup>16</sup> Lid involvement may be seen in up to 5% of patients and may be associated with a lid abscess as a result of secondary bacterial infection (Fig. 83.1).<sup>17</sup> Treatment options include cryotherapy, curettage, incision, and excision.<sup>18</sup>

### Lid Infections

Severe blepharitis, sty, and lid ulceration may occur as initial manifestations of ocular involvement in AIDS.<sup>19</sup> Treatment with antibiotics along with lid hygiene needs to be continued for a longer duration in these patients than in seronegative individuals.



**Fig. 83.1:** Molluscum contagiosum on the lids and face in a HIV-positive patient.

### Conjunctival Squamous Cell Carcinoma

Conjunctival squamous cell dysplasia and neoplasia have been associated with HIV infection and AIDS in the sub-Saharan African population.<sup>20</sup> Squamous cell carcinoma was reported in a healthy young patient, who was later found to be positive for HIV-2 infection.<sup>21</sup> Any rapidly growing mass on the conjunctiva should arouse the suspicion of an immunosuppressive condition.

### Keratoconjunctivitis Sicca

Keratoconjunctivitis sicca occurs in 10–20% of patients with HIV infection.<sup>22</sup> This is probably secondary to the destruction of the primary and secondary lacrimal glands as a result of either HIV mediated inflammation or an autoimmune pathology. Treatment is directed towards providing symptomatic relief using artificial tear substitutes and lubricating ointments.

### Infective Keratitis

A wide spectrum of ocular infections is associated with HIV infection. Viral keratitis is more common as compared to bacterial and fungal infections. In certain geographic areas, fungal keratitis has been reported to be an indirect indicator of HIV infection.<sup>23</sup> Recurrence is common for both varicella zoster virus keratitis and herpes simplex keratitis. Treatment for varicella zoster is with oral acyclovir 800 mg 5 times daily for 7–10 days or famciclovir 500 mg 3 times daily. Infection with herpes simplex virus requires half to one-fourth of the dose.

Microsporidia are obligate intracellular parasites known to cause gastroenteritis, sinusitis, and pneumonitis in HIV infected patients. Ocular involvement is in the form of a diffuse superficial punctate keratopathy associated with conjunctivitis.<sup>24</sup> Diagnosis is made by the characteristic staining of the intracellular organisms. Treatment is usually with topical fumagillin, pentamidine isethionate, and oral itraconazole or albendazole.

### Anterior Uveitis

Anterior uveitis is less common than posterior or panuveitis.<sup>25</sup> Drugs like cidofovir and rifabutin can also cause uveitis due to their toxicity.

### Ophthalmic Kaposi Sarcoma

Kaposi sarcoma most commonly involves the anterior segment of eye. Generally, ophthalmic Kaposi sarcoma is indolent. Ocular tumor growth can result in severe damage to the ocular adnexa and ocular surface. Involvement of the eyelids can cause significant disfigurement and lid dysfunction. Trichiasis can develop due to mechanical ectropion or entropion. Lagophthalmos and trichiasis can cause profound irritation, dryness, and infections leading to corneal scarring.<sup>26</sup>

Large lid tumors can also induce irregular corneal astigmatism. Conjunctival involvement may result in recurrent subconjunctival hemorrhages. Ultimately, vision could be lost due to lid

dysfunction, corneal surface changes or due to visual obstruction. The lesions are purplish-red to bright red and highly vascular with surrounding telangiectatic vessels. They may be macular, plaque-like or nodular.

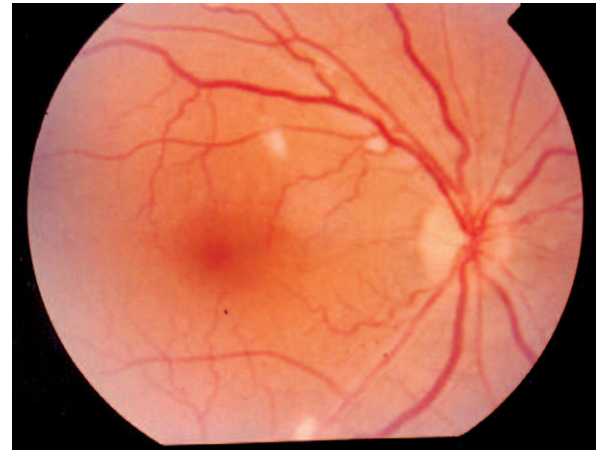
DNA sequences of human herpes virus 8 (HHV 8) have been detected in Kaposi sarcoma in patients with and without HIV infection.<sup>27</sup> HHV 8 is considered to be quite uncommon in the Indian subcontinent. This could be the probable reason for the low prevalence of Kaposi sarcoma in AIDS patients in India. In a large series of 100 HIV positive cases from India, Kaposi sarcoma was not found in any.

## POSTERIOR SEGMENT LESIONS

Posterior segment lesions involve the retina, choroid or optic nerve. Sometimes, the lesions may involve more than one structure. More than 50% of the patients with ocular involvement have lesions in the posterior segment.<sup>12</sup> Some of these lesions can threaten vision but patients may even be asymptomatic. When the lesions do not involve the posterior pole, the usual symptoms include floaters, flashes of light, visual field defects, and dimness of vision. In India, as routine ophthalmic check-up is not a norm, in many instances patients are seen in an advanced stage. Posterior segment lesions are divided into the following categories.

### HIV Retinopathy

HIV related retinal microangiopathy was the most common ocular lesion in patients with AIDS before the introduction of highly active antiretroviral therapy (HAART). It was detected in almost 50% of the cases during the late stages of HIV infection.<sup>12</sup> Presently, due to the early treatment of HIV, the prevalence of retinopathy has declined.<sup>28</sup> HIV retinopathy is a noninfectious microvascular disorder characterized by cotton-wool spots, microaneurysms, retinal hemorrhages, telangiectatic vascular changes, and areas of capillary nonperfusion. Cotton-wool spots occur in approximately 25–50% of the patients with advanced HIV disease and are the earliest and most consistent findings in HIV retinopathy (Fig. 83.2). A cotton-wool spot is caused by a circulatory disturbance in a tiny area of the retina. Usually, the spots are distributed along the vascular arcades. The condition may mimic diabetic and hypertensive retinopathy. However, hard exudates observed in diabetic retinopathy are not present in HIV retinopathy. In addition, cotton-wool spots in HIV retinopathy are much smaller in size and persist for a shorter period. A patchy involvement of the retinal capillaries is seen in AIDS, in contrast to a widespread capillary disease seen in preproliferative and proliferative diabetic retinopathy. The average time for the disappearance of cotton-wool spots in HIV retinopathy is 6–12 weeks.<sup>29</sup> They are not vision threatening, although in advanced HIV disease they can produce small visual field defects. One can also distinguish cotton-wool spots from hypertensive retinopathy as the latter has vascular changes like arteriolar narrowing. In addition, they can be confused with early cytomegalovirus (CMV) retinitis lesions. Benign cotton-



**Fig. 83.2:** Showing cotton-wool spots along the retinal vessels in a HIV-positive patient.

wool spots can be differentiated by their smaller size, superficial location, lack of progression, and tendency to resolve over weeks to months. In HIV-seropositive patients, hemorrhages may involve both the nerve fiber layer and the deeper retina and may appear as flame-shaped, dot or blot hemorrhages. Telangiectatic vascular changes may be seen in patients with HIV disease and are often associated with microaneurysms.

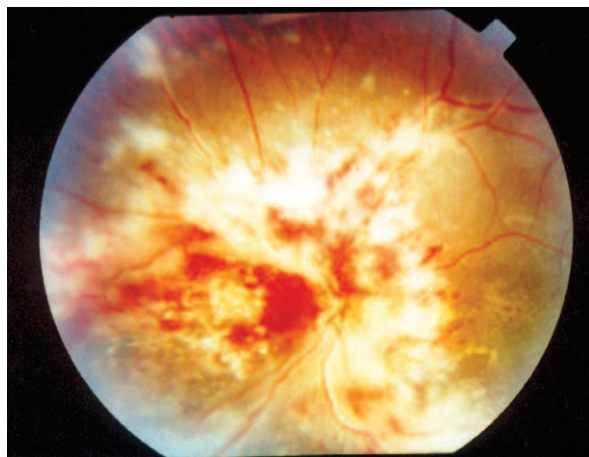
### Opportunistic Infections

An increasing number of infections of the retina and choroid have been reported in individuals with advanced HIV disease. Although a number of these infections can also be seen in immunocompetent patients, it is important to remember that there may be significant differences in the clinical presentation in HIV-infected patients who present with lesser inflammation, take a longer time to respond to therapy, and have a higher chance of recurrence. Multiple foci of infection, bilateral infection as well as more than one infection in the same eye may occur in HIV-infected patients. Finally, new not yet described infections of the retina and choroid are likely to be encountered in HIV-seropositive patients in the future. A strong correlation exists between the level of immunosuppression (CD4+ cell count) and the appearance of opportunistic infections.<sup>30</sup>

### Cytomegalovirus (CMV) Retinitis

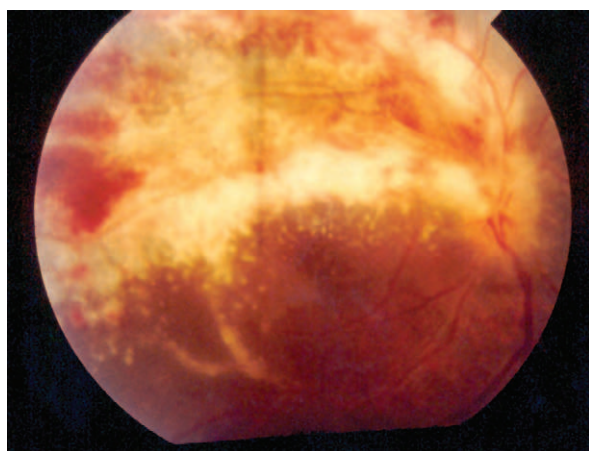
Cytomegalovirus is a species-specific DNA virus classified in the herpes group of viruses. CMV retinitis is the most common ocular infection in patients with HIV disease and occurs in 15–40%,<sup>31</sup> particularly when the CD4+ cell count is less than 100 cells/ $\mu$ L.<sup>32</sup> Earlier it was bilateral in 30–50% of patients; although that rate may now be lower as the administration of anti-CMV medication almost always prevents the onset of retinitis in the fellow eye.<sup>33</sup> CMV disease affecting the eye, however, tends to occur only in the developing foetus or in immunocompromised patients. CMV infection of the retina leads to the viral invasion of retinal cells with resultant retinal necrosis. The classic description of CMV retinitis



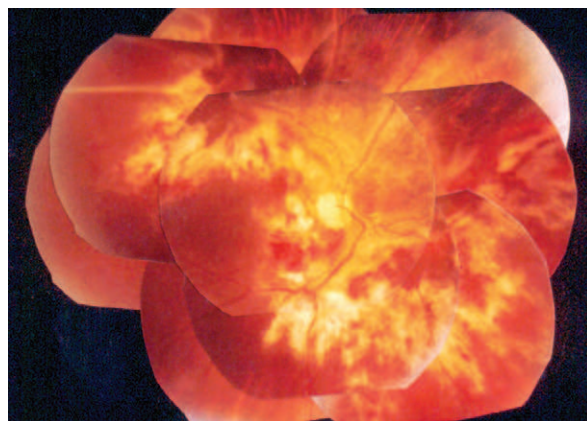


**Fig. 83.3:** CMV retinitis in AIDS patient.

is one of scattered yellow-white areas of necrotizing retinitis with a variable degree of hemorrhage and mild vitreous inflammation (Fig. 83.3). Indeed, some authors have described this as “cottage cheese with catsup” or “pizza pie” retinopathy. Initially presenting as small white, granular patches, these areas continue to enlarge if left untreated. Active lesions show a white retinal necrosis usually associated with hemorrhage. Often, the retinitis follows a perivascular distribution (Fig. 83.4). The advancing edge of these lesions is usually very sharp and spreads contiguously. Typically, over several weeks, untreated lesions progress to full-thickness necrosis with resultant retinal gliosis and pigment epithelial atrophy (Fig. 83.4).<sup>34</sup> The pathway of expanding lesions can be predicted by the appearance of venous sheathing or white dots distal to the leading edge, indicative of direct cell-to-cell spread of infection. Expanding lesions often take on a brushfire border, with the active edge of whitening spreading from the previously infected area. With involvement limited to the peripheral retina, patients either have no subjective complaints, or may complain of floaters. If retinitis begins in the posterior pole, the patient may notice a visual field deficit. The possible mechanisms for visual loss are



**Fig. 83.4:** Active CMV retinitis in AIDS patient.



**Fig. 83.5:** Tractional retinal detachment in a patient of CMV retinitis.

direct retinal necrosis by infection, optic nerve involvement and retinal detachment. CMV retinitis may result in either serous, rhegmatogenous, or tractional retinal detachment, although the latter is much more common (Fig. 83.5). Rhegmatogenous retinal detachment has been reported in 13.5–29% of patients with CMV retinitis and may occur during the active or healing phase of the disease.<sup>34</sup> These detachments are particularly difficult to repair using standard retinal detachment surgery. Other findings associated with CMV retinitis include perivasculitis, vascular attenuation and vessel closure, as well as vitritis, anterior uveitis, and papillitis (Fig. 83.6).

Approximately 6% of patients with CMV retinitis are estimated to have frosted branch angiitis,<sup>38</sup> an entity originally described by Ito et al.<sup>36</sup> It is essentially a severe form of vasculitis, which affects the entire retina. Although both arteries and veins are affected, venules tend to be affected more. Frosted branch angiitis may be an idiopathic disorder or can be associated with ocular and systemic diseases. AIDS retinitis and *Toxoplasma* chorioretinitis are the most frequent ocular associations, while systemic lupus erythematosus (SLE), Crohn disease, large cell lymphoma, and



**Fig. 83.6:** Healed CMV retinitis.





**Fig. 83.7:** Frosted branch angiitis.

acute lymphoblastic leukemia are the systemic disorders associated with frosted branch angiitis (Fig. 83.7).

### **Varicella Zoster Virus Disease**

**Acute Retinal Necrosis (ARN)** It has been described in otherwise healthy adults of either sex of any age, but is more common in immunocompromised individuals, including those with AIDS.<sup>11</sup> In a majority of the patients, the retinal necrosis syndrome appears to be caused by VZ virus, however, HSV has also been implicated as a causative agent.

Clinically, the syndrome is insidious in onset, with a mild anterior uveitis accompanied by blurred vision. However, sometimes ARN may present with severe ocular pain. Examination of patients during the early stage of this syndrome reveals evidence of posterior and anterior uveitis, keratic precipitates, vitreous cells, and clouding of the ocular media. The retinitis is often seen first in the peripheral fundus but within a matter of days to weeks, may progress to a dramatic whitening of the peripheral retina and retinal pigment epithelium in multifocal and coalescent patches. Vasculitis involving both arteries and veins is a prominent feature, usually associated with areas of hemorrhage and vascular occlusion. An acute swelling of the optic nerve head and macular edema are often present during the active phase of the disease. If the contralateral eye is also involved, the clinical course is similar.

The subsequent course is one of resolution of the retinal lesions with the regression of the retinal whitening, followed by mild pigmentary scarring of the retina with sharp demarcation between the normal and affected areas. Regression begins at the outer margin of the lesions and moves centrally, this may be quite rapid, taking only 2–3 weeks. A late sequela is the development of vitreoretinal traction due to organization of the vitreous. This traction leads to retinal tears, and rhegmatogenous retinal detachment. Clinical differentiation between the various HSV types and VZV is often not possible, however, there are indications that retinitis due to HSV-2 begins at the posterior pole.<sup>37</sup>

**Progressive Outer Retinal Necrosis (PORN)** It is a recently recognized variant of necrotizing herpetic retinopathy representing

a distinct form of ARN, developing in patients with AIDS or other immunosuppressive conditions.<sup>38</sup> It is characterized by early macular retinitis in the presence of little or no intraocular inflammation. There is rapid progression with the development of lesions in the mid and peripheral retina with no consistent direction of disease spread unlike that seen in cases of ARN. Unlike ARN and typical CMV retinitis, which involve the full thickness of the retina, this condition is characterized by deep retinal opacification without granular borders, giving the impression of an “outer retinitis.” With progression there is a clearing of the areas around the retinal vessels, which has been described as a “cracked mud” appearance. These areas are either regions of perivascular retinal sparing or this pattern may represent an early removal of necrotic debris and edema from retinal tissues adjacent to the vasculature (Fig. 83.8). As infected areas of the retina become necrotic, large retinal breaks occur leading to rhegmatogenous retinal detachment in a majority of the affected eyes, contributing to the overall poor prognosis. Diagnosis of PORN is always clinical, based on its characteristic appearance as described. However, it closely mimics ARN and CMV retinitis (Fig. 83.9).

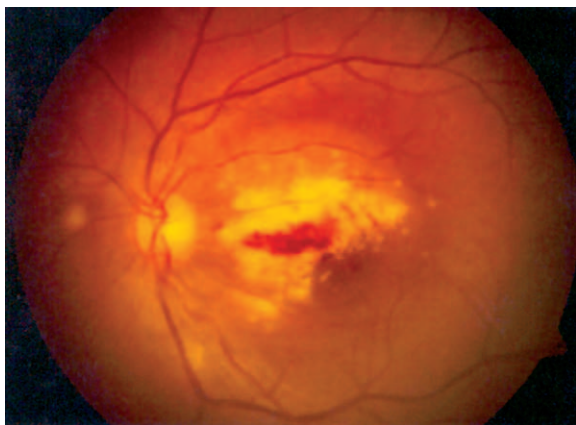
### **Treatment of Viral Retinitis**

The treatment of viral retinitis may be systemic, local or a combination of the two. The following drugs are in use:

**Ganciclovir** It is a nucleoside analog that acts as a competitive inhibitor and faulty substrate for CMV DNA polymerase. Ganciclovir inhibits all herpes viruses, including CMV by preventing DNA elongation. An induction dose of 5 mg/kg every 12 hours for 14–21 days should be followed by a maintenance dose of 5 mg/kg/day, indefinitely.<sup>39</sup> It takes 2–3 weeks before the clinical effect is apparent and 3–6 weeks before complete healing is achieved. Since ganciclovir is virustatic, recurrence often occurs within 10–21 days of discontinuation of therapy. The major side effect is neutropenia (5%–40%), which can be managed with granulocyte colony stimulating factor (G-CSF) 300 µg daily. Other adverse effects include thrombocytopenia, anemia, nausea, vomiting, and elevated liver enzymes.



**Fig. 83.8:** Progressive outer retinal necrosis in AIDS patient.



**Fig. 83.9:** CMV retinitis involving posterior pole.

**Foscarnet** It is a pyrophosphate analog that inhibits DNA polymerase (of CMV and other herpes viruses HSV-1, HSV-2, VZV, and Epstein-Barr virus) and reverse transcriptase by directly affecting the pyrophosphate binding site. This agent is also virustatic and it has an intrinsic anti-HIV effect that may be beneficial in reducing the HIV viral load in combination with other antiretroviral agents. An induction dose of 90 mg/kg twice a day for 14–21 days is followed by a maintenance dose of 90–120 mg/kg/day indefinitely.<sup>40</sup> Cessation of retinal lesion advancement and resolution of the acute inflammation is usually seen within 4 weeks. The major side effects are nephrotoxicity and hypocalcemia, causing arrhythmias and seizures. Electrolyte imbalance leading to hypercalcemia and hyperphosphatemia or hypophosphatemia may occur.

A combination of foscarnet and ganciclovir is more effective than monotherapy in the treatment of recurrent or resistant viral retinitis.<sup>41</sup> Unfortunately, combination intravenous therapy necessitates multiple intravenous infusions daily and has a marked negative effect on patient's lifestyle.<sup>42</sup>

**Acyclovir** It is a nucleoside analog that has potent activity against HSV-1 and 2, and VZV. The recommended intravenous dose is 1500 mg/m<sup>2</sup>/day divided into 3 daily doses for 7–10 days. This should be followed by an oral therapy of 800 mg 5 times daily for VZV and 400 mg three times daily for HSV-1 and 2 for 14 weeks duration. Complete regression occurs within 4 weeks and chances of involvement of the fellow eye are also reduced with this therapy.

**Intravenous Cidofovir** It is a nucleotide analog, which does not require phosphorylation by viral encoded enzymes. It is active in uninfected cells, can act preemptively, and may retain activity against ganciclovir-resistant strains of CMV. An induction dose of 5 mg/kg intravenously every week for 2 weeks followed by a maintenance dose of 5 mg/kg every 2 weeks, indefinitely, is recommended.<sup>43</sup> Increased proteinuria and elevations in serum creatinine are the major dose limiting toxicities.<sup>44</sup> Ocular complications include transient iritis (up to 40% cases) and ocular hypotony (12% cases).<sup>45</sup> However, since decreased intraocular pressure is common and usually clinically insignificant in patients

with advanced AIDS, the clinical relevance of this finding is not clear.<sup>46</sup> The iritis responds well to topical steroids and cycloplegics.

**Ganciclovir Intraocular Implant** The ganciclovir implant is a sustained-release drug delivery device that contains about 4.5–6 mg of ganciclovir. A pellet of ganciclovir salt is first coated with a permeable layer of polyvinyl alcohol, followed by an impervious coating of ethylene vinyl acetate, and then by another coating of polyvinyl alcohol. It is placed into the vitreous cavity through a 5–6 mm incision in the pars plana and sutured to the sclera. The drug diffuses into the vitreous cavity by passive diffusion at the rate of 1 µg/hr over a 6–8-month period. After that, the device is usually surgically removed and replaced with a new device. The intravitreal levels attained by this drug are over twice those after intravenous administration, and this appears to be associated with a lower incidence of resistance and progression of retinitis. Adverse events include retinal detachments (12%), endophthalmitis (1.7%), and transient vitreous hemorrhage (7.8%). However, as with all local treatments, there is a risk of CMV disease in the fellow eye (up to 40% cases) and even extraocular CMV disease (10.3%).<sup>47</sup>

**Intravitreal Ganciclovir** Ganciclovir was the first anti-CMV compound administered as an intravitreal injection. The dose varies from 200–2000 mg/0.1 mL. These injections are given twice a week. They are usually tolerated well, are highly effective (Fig. 83.10), and relatively inexpensive. The main adverse effects include endophthalmitis, retinal detachment, and vitreous hemorrhage.<sup>48</sup>

### **Toxoplasma Retinochoroiditis**

*Toxoplasma gondii*, a protozoon, affects about 10% of the patients with AIDS. However, Toxoplasma retinochoroiditis is relatively rare and accounts for only 1% of AIDS related retinal infections.<sup>49</sup> It produces a necrotizing retinitis similar to CMV retinitis. Ocular toxoplasmosis is much less common in HIV infected patients than Toxoplasma encephalitis, probably due to difference in parasite load. There can be a single lesion or multifocal lesions in one or both eyes and broad areas of retinal



**Fig. 83.10:** Regression of CMV retinitis after intravitreal ganciclovir.



necrosis. The retina appears to have a hard and “indurated” appearance with sharply demarcated borders and small retinal hemorrhages. Progression is generally slow. CNS lesions are seen in 29–50% of HIV infected patients with ocular toxoplasmosis. Serologic diagnosis is often difficult due to a depressed antibody response.

### Mycobacterial Infection

Extrapulmonary and disseminated tuberculosis is seen more commonly in HIV positive patients. However, choroidal tuberculosis has not been so commonly reported. It is possible that many cases of choroidal tuberculosis remain asymptomatic and probably regress with the anti-tubercular treatment for extraocular tuberculosis. It usually presents as multifocal choroiditis with discrete yellow choroidal lesions mainly at the posterior pole. It may be associated with an exudative retinal detachment with variable vitreous inflammation.

Ocular tuberculous manifestations are the same as in immunocompetent patients. These patients require longer therapy because of their immunocompromised status and the inadequate absorption of drugs due to malabsorption associated with AIDS. Disseminated choroiditis is the most common manifestation reported.

Infection with atypical mycobacteria like *Mycobacterium avium-intracellulare* may occur in about 15–20% of the patients with AIDS. It has been demonstrated in choroid of the eyes removed at autopsy in about 1–6% of the patients. Both, *Pneumocystis jiroveci* and *M. avium-intracellulare* have also been demonstrated in the choroid of the same patient.<sup>50</sup>

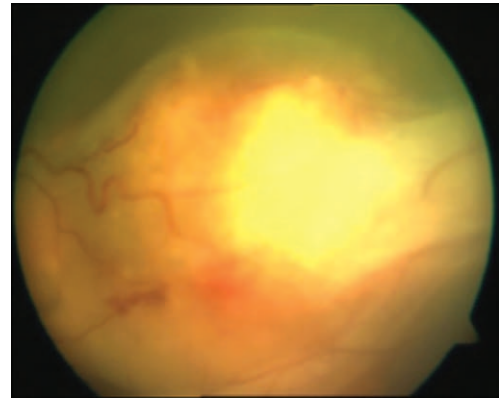
**Ocular Tuberculosis** HIV/tuberculosis coinfection is of special concern especially in developing nations where background rates of TB are among the highest in the world. Ocular TB can present with protean manifestations, including choroiditis, choroidal granulomas (Fig. 83.11), chorioretinitis, endophthalmitis, subretinal abscess, and panophthalmitis.

Choroidal tuberculosis has not been found to be as common as systemic tuberculosis in patients with AIDS. No definite correlation of the occurrence of ocular tuberculosis with CD4 counts was found in our study, the largest series of patients with ocular TB in the world.<sup>51</sup>

### Fungal Infections

Candida and Cryptococcus are the most common intraocular fungal infections. Isolated candidal endophthalmitis is remarkably uncommon in contrast to systemic candidal infection in HIV-positive patients. Fluffy-white chorioretinal lesions along with snowball like masses are usually seen. Other lesions are creamy-white multiple chorioretinal lesions with an overlying vitreous inflammation.

*Cryptococcus neoformans* is the most common neurologic fungal infective agent in AIDS. It usually causes chronic meningitis, which may result in papilloedema, optic neuropathy, and cranial nerve palsy.



**Fig. 83.11:** Color fundus picture showing tuberculous subretinal abscess.

### Pneumocystis Jiroveci Choroidopathy

*Pneumocystis jiroveci*, a unicellular protozoan, is the most common opportunistic infection in patients with AIDS presenting as pneumonitis. *P. jiroveci* spreads to the choroidal layers through the hematogenous route. *P. jiroveci* choroidopathy is often seen in the patients treated with aerosolized pentamidine for PCP prophylaxis. It may be an initial sign of disseminated life threatening *P. jiroveci* infection.

Patients often do not have visual symptoms. The fundus shows multiple yellowish white, usually round, subretinal plaques distributed throughout the posterior poles. The lesions can coalesce on progression. Typically there is no vitreous inflammation. Fundus fluorescein angiography shows an early hypofluorescence of the lesions with delayed staining. Histopathologic studies of the eyes removed at autopsy revealed multiple eosinophilic, acellular, frothy, and vacuolated material. Special stains may demonstrate mature cysts of *P. jiroveci*.<sup>52</sup> *P. jiroveci* choroidopathy indicates a poor prognosis. Average survival after diagnosis is about 4 months.

## ORBITAL LESIONS

### Orbital Cellulitis

Aspergillosis and mucormycosis are the common orbital infections seen in patients with AIDS. Aspergillosis presents as a nongranulomatous disease with abscess formation and lack of fibrosis. This is in contrast to the slow granulomatous and fibrotic response in immunocompetent hosts. The classic presentation of orbital mucormycosis is severe unilateral headache, nasal stuffiness with granular or purulent discharge, facial or eyelid edema, fever, and leukocytosis.

## NEURO-OPHTHALMIC LESIONS

In advanced HIV disease, the brain is involved either by direct infection with HIV or with opportunistic infections. Neuro-ophthalmic complications occur in 10–15% of HIV-infected patients.<sup>53</sup> Since over 50% of the human brain is concerned in some way with the act of seeing, the eyes may show signs of brain



involvement. Blurred vision, problems with eye movement, or double vision may indicate some pathology in the brain. Nonviral infections are responsible for half of the CNS abnormalities; toxoplasmosis and cryptococcal infestation being the most common. Cryptococcal meningitis can present with papilloedema with peripapillary retinal hemorrhages,<sup>54</sup> optic atrophy, and ophthalmoplegia.<sup>55</sup>

## NEOPLASMS

Degradation of the immune system predisposes to specific malignancies like Kaposi sarcoma, non-Hodgkin lymphoma (NHL) and squamous cell carcinoma in HIV patients.

High-grade lymphoma is an AIDS defining disorder. Orbital and intraocular involvement is uncommon and is seen in less than 1%.<sup>56</sup> The clinical appearance of intraocular lymphoma is multifocal yellow-white chorioretinal lesions associated with vitritis. It may be associated with primary CNS lymphoma.

## Ocular Manifestations in HIV/AIDS in the Era of HAART

The advent of potent antiretrovirals has had a profound effect on the ophthalmological manifestations of patients with AIDS. As these drugs lead to an improvement in the immune function, patients have fewer opportunistic infections.<sup>12</sup> It has been estimated that the frequency of new CMV retinitis cases has decreased by 80% or more. Other HIV related ophthalmic disorders like Kaposi sarcoma are also seen infrequently. Those patients who have never received potent antiretroviral therapy, should be given a combination of agents in an attempt to improve immune function. In those with the evidence of immune reconstitution (elevated CD4+ T-lymphocyte counts, lower levels of HIV in the blood), control of CMV retinitis becomes easier and in many cases it is possible to discontinue specific anti-CMV therapy. Immune reconstitution may take 8 weeks or longer. Thus, aggressive anti-CMV therapy is required during this period. There are no well-established criteria to identify patients with sufficient immune recovery to allow the withdrawal of specific anti-CMV therapy.

An emerging problem among patients with CMV retinitis is “immune recovery uveitis.” As immune function improves following the initiation of potent antiretroviral therapy, some patients will develop heightened intraocular inflammatory responses, presumably to CMV antigens. Immune recovery uveitis is characterized by anterior chamber cells and a vitreous haze. Although the vitreous humor reaction may be transient, patients may be left with complications of inflammation, such as persistent macular edema, epiretinal membranes, and decreased vision.<sup>57,58</sup> Inflammation and macular edema respond to corticosteroid therapy, and possibly to nonsteroidal anti-inflammatory agents, but recovery of normal vision is rarely achieved in patients with macular edema. The frequency of immune recovery uveitis is not known, estimates range from 20% to 60%.

Patients with HIV can develop ocular manifestations at any point of their illness, so they need regular ophthalmological

examination. With the advent of HAART, the spectrum of ocular diseases (like opportunistic infections of other organ systems) is changing. Hopefully, these diseases will be more and more uncommon or less severe in the future.

### Summary

The incidence of ocular complications in HIV-infected individuals has decreased with the advent of highly active antiretroviral therapy (HAART). In spite of adequate and regular HAART, patients can still develop vision-threatening ocular lesions that can affect quality of life and hamper the ultimate goal of rehabilitation of the individual. Multiple pathogens found in the same individual or with an atypical presentation can give a clue to the diagnosis of the underlying HIV-related systemic disorder. Anterior segment and adnexal involvement in these patients may even be the primary presentation of AIDS.

Viral infections, such as herpes zoster, herpes simplex and molluscum contagiosum are more common. Patients with herpetic eye disease in AIDS may need long-term maintenance therapy. Herpes zoster ophthalmicus is seen relatively more commonly in India even in the HAART era.

Although the incidence of CMV retinitis has fallen with ART, it is still the most common ocular opportunistic infection. Other infections such as tuberculosis, toxoplasmosis, other herpes viruses and treponema can all cause damaging eye lesions.

Early identification and treatment of posterior segment manifestations is even more important as they can cause irreversible blindness.

Patients on HAART can develop severe inflammatory reaction due to immune reconstitution inflammatory syndrome (IRIS), which can cause severe ocular morbidity. With HAART newer manifestations of known lesions occur. Hence, it is important that ophthalmologists are aware of this new emerging phenomenon and treat them appropriately.

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## Introduction

Sexually transmitted infections (STIs) are the most common infectious disease of public health importance. Each year there are an estimated 340 million new cases of curable STIs, as well as many millions of incurable viral STIs, including 5 million new human immunodeficiency virus (HIV) infection diagnosed globally (WHO). Over 30 different bacteria, viruses, and parasites are associated with STIs not only causing acute morbidity but also leading to chronic complications.

Most cases of HIV have been sexually transmitted. The link between STIs and the sexual spread of HIV is clear. STIs act as cofactors and facilitators for HIV transmission (epidemiological synergy).<sup>1</sup> The sexual HIV transmission is affected by a number of factors including the presence of an untreated STIs and the stage of HIV infection.

STIs occur frequently in HIV-infected persons but the management of STIs in these patients continues to challenge healthcare providers. Although these pathogens can cause a variety of easily recognized clinical syndromes, most are asymptomatic. For this reason, HIV-infected patients should be assessed for STI-related risk behaviors at every visit and screened annually for common STIs and more frequently if risk behaviors are reported. Both behavioral and biomedical interventions have a major role in protecting individuals from HIV and STIs. The prompt and appropriate treatment for STIs reduces individual risk of HIV infection. Since all STIs and HIV are preventable a high-quality STI programs are critical for controlling the transmission of HIV.

## STIs in HIV Infection

HIV alters the clinical presentation of STIs, their natural history, their relative prevalence and in some cases, their susceptibility to infection. HIV and STIs share common behavioral determinants; however the association is much more complicated. Genital ulcer diseases (GUD) and other STIs facilitates the sexual transmission of HIV. In both men and women STIs boost HIV shedding in the genital tract, which amplifies HIV infectiousness. The

presence of STIs also increases susceptibility to HIV by recruiting HIV-susceptible inflammatory cells to the genital tract as well as by disrupting mucosal barriers to infection. HIV infection also causes a rapid depletion of immune cells in semen. This immune depletion could render HIV-positive men more vulnerable to STIs, further increasing the risk of onward HIV transmission.<sup>2</sup>

Studies have estimated the overall risk for acquiring HIV in patients with STDs, and the odds ratio is: GUD 3.0–18, chlamydial urethritis 3.0–6.0, gonococcal urethritis 3.5–9.0, trichomoniasis 3, and genital herpes 2.<sup>1</sup> In a study done on a large cohort of patients attending STD clinic in Pune, India,<sup>3</sup> patients who had GUD were more than 4 times as likely to seroconvert as those without genital ulcers. For an HIV-negative person genital ulcer provides a portal of entry and for HIV-infected persons it provides a portal of exit. Presence of increased number of activated CD4+ cells in the ulcer further enhances the transmission or acquisition of HIV. Investigators in Kenya and the Ivory Coast found that HIV-1 RNA was significantly increased in cervicovaginal fluids of patients with STIs. Ghys et al.<sup>4</sup> noted a significant increase in detection of HIV-1 RNA in cervicovaginal secretions from patients with cervicovaginal ulcers. HIV-1 RNA decreased from 42% to 21% 1 week after treatment for STI, but no changes were observed in women whose STIs were not cured. The impact of nonulcerative STIs on the HIV epidemic could be potentially much greater because of high prevalence of nonulcerative STIs compared in most populations. While genital ulcers increase HIV transmission bidirectionally for both receptive and insertive sex partners, nonulcerative STIs like gonorrhea, chlamydial urethritis, or trichomoniasis increase risk primarily for the receptive partners.<sup>5</sup> Ho et al.<sup>6</sup> showed that *Chlamydia trachomatis* increases the replication of HIV-1, probably, through the generation of reactive oxygen products secreted by granulocytes. Chlamydial infection also causes secretion of cytokines that could affect the replication of HIV-1 and the number of receptive cells. Asymptomatic urethritis is independently associated with seminal HIV RNA shedding. Moss et al.<sup>7</sup> detected HIV-1 RNA in the urethra more frequently in patients with coexistent gonococcal urethritis than

in controls or in patients who had been treated. Cohen et al.<sup>8</sup> studied 86 HIV-seropositive patients with urethritis and found an 8-fold increase in secretion of HIV-1 RNA in semen when compared to a control group and the concentration of HIV-1 RNA in semen fell 2 weeks after appropriate antibiotic therapy to values not significantly different from those in controls.

Mostad et al.<sup>9</sup> noted a significant increase in detection of HIV-1 in samples from women with gonococcal cervicitis and vaginal candidiasis, but not in those with trichomoniasis or chlamydial infection. Increase in detection of HIV-1 RNA was also observed in pregnant women with cervical discharge. Increased HIV shedding is also seen in women with cervical ectropian, ranging from 15% with no cervical ectropian to 83% for with more than 50% ectropian.<sup>10</sup> STIs might increase the number of cells receptive to HIV-1. In addition to the increase in viral shedding an increase in CD4+ cells have also been demonstrated in genital secretions from women with STIs.<sup>11</sup>

## SYPHILIS

Since the emergence of the AIDS epidemic, syphilis has attracted renewed attention. The incidence of syphilis has also risen sharply in recent years mainly due to complacency among both MSM and heterosexuals regarding HIV infection, the ability to connect with sex partners online through Internet sites and the positive effects of antiretroviral therapy on quality of life.<sup>12</sup> The change in sexual behavior of HIV-infected persons such as seeking sex partners who are HIV-infected (serosorting) are also rising, further contributing to the epidemic.

The natural history of syphilis could be altered in the presence of HIV. Syphilis not only assumes unusual clinical presentations but also exhibit an unusual clinical course.<sup>13</sup> In coinfecting patients, syphilis may masquerade as other infections, including herpes and fungal infections and noninfectious dermatologic conditions.

Atypical presentations of early syphilis, early involvement of the central nervous system (CNS) and more frequent cases of neurosyphilis, rapid progression to tertiary syphilis, treatment failures and altered response to serological tests have been reported in coinfecting patients. Reactivation of syphilis is also seen in HIV-infected individuals with the possibility of relapse of secondary syphilis and subsequent transmission to sexual partners. However, despite the number of reports of unusual features, most HIV-infected patients present similarly to non-HIV-infected patients.

## Primary Syphilis

Primary chancre in HIV-infected patients may present as multiple chancres that are larger, deeper, and heal more slowly. Various morphological forms including gangrenous, phagedenic, and erosive are reported.<sup>14</sup> Primary chancre may still be present when lesions of secondary syphilis appear. This could be either due to rapid progression of the disease or delayed healing of primary lesion, or both.<sup>15</sup> Sometimes the tissue destruction caused by the chancre can be mistaken for donovanosis. Mixed infections with other STIs, mainly HSV, are not uncommon.

## Secondary Syphilis

Signs of secondary syphilis in HIV-infected patients may develop sooner. General symptoms like fever, headache, weakness, and ulcerative lesion (malignant syphilis) characterized by rupia like skin lesions are about 60 times more frequent in HIV-positive individuals than HIV-negative individuals.<sup>16</sup> Condyloma lata is also more common than in non-HIV-infected patients.

The rash can be more widespread and lasts longer. The simultaneous presence of all morphological lesions like papules, nodules, pustules, ulcers, and crusted forms is seen. Altered morphological forms such as palmoplantar keratoderma, livedo vasculitis of trunk, and vesicular and hyperkeratotic forms have also been described.<sup>17,18</sup> Clinical variants of secondary syphilis (corymbose, annular, nodular, or pustular forms) are also more frequently seen in HIV-seropositive patients.

Some clinical forms of secondary syphilis can mimic lupus vulgaris, leprosy, leishmaniasis, and pyoderma. Secondary syphilis should be considered in the differential diagnosis of inflammatory cutaneous disorders in HIV-positive individuals. The likelihood of unusual presentations in secondary syphilis is greater when CD4+ cell count falls below 150/mm<sup>3</sup>. CNS and ocular involvement are not uncommon in coinfecting patients. About 5% of patients of secondary syphilis develop uveitis,<sup>19</sup> which is bilateral in half of these cases. Orbital inflammation, conjunctival hyperemia, optic neuritis, chorioretinitis, and retinal vasculitis with retinal hemorrhage may also occur.

## Tertiary Syphilis

The ulcerative or nodular manifestations of benign tertiary syphilis are known as gummata. A gumma is thought to represent an enhanced immune response to *T. pallidum*, as organisms are present in low numbers in these lesions. Gumma arises either from reactivation of syphilis present in untreated or inadequately treated individuals, or from reinfection in previously sensitized individuals. There is evidence that *T. pallidum* persists in some patients who have received what is regarded as adequate therapy for syphilis. It has been suggested that *T. pallidum* persists in a state of commensality, with the potential to recover its virulence with immunosuppression. It may also be seen in immune-reconstitution syndrome associated with highly active antiretroviral therapy (HAART).<sup>20</sup> Gummatous lesions involving multiple organs including the brain may occur in HIV-infected patients<sup>21</sup> nevertheless syphilitic gumma remains uncommon in HIV-positive individuals.

Cardiovascular involvement may result in aneurysms, coronary artery stenosis, or aortic regurgitation. Although rare in antibiotic era rapidly evolving cases of syphilitic aortitis have been reported in HIV-infected patients.<sup>22</sup>

## Neurosyphilis

Concurrent HIV infection has a profound impact on neurological involvement in syphilis. Rapid progression of early syphilis to

neurosyphilis is also seen. HIV infection itself produces numerous neurological abnormalities. HIV impairs cellular immunity, macrophage function and peripheral CD4+ lymphocytes in these patients have decreased ability to assist B cells in the production of immunoglobulins. These functional immunological abnormalities will impair the host defence against syphilis and facilitate its progression. Meningeal inflammation induced either by HIV or syphilis will facilitate entry of either agent into the CNS.<sup>23</sup> Every patient with primary syphilis develops spirochetemia and is at risk of seeding the CNS and developing neurosyphilis. The immunological response of a patient has an important role in controlling the infection, even in presence of adequate antibiotic therapy.<sup>24</sup>

Neurologic manifestations of syphilis, including syphilitic meningitis, meningovascularitis, cranial nerve palsies, (second and eighth cranial nerves were most commonly involved) optic neuritis, myelitis, stroke and cerebral gummas are more common in HIV-infected patients.<sup>25–28</sup> Neurosyphilis should be distinguished from other opportunistic infections like CNS tuberculosis, cryptococcosis, or toxoplasmosis.

### Diagnosis of Neurosyphilis in HIV-Infected Patients

Routine CSF examination for HIV-infected patients with early syphilis is not recommended. Studies have shown that both a CD4+ cell count <350 cells/mm<sup>3</sup> and a serum RPR titer >1:8 are independent predictors of central nervous system invasion by *T. pallidum*.<sup>34</sup> Study by Marra et al. found an RPR serum antibody level ≥1:32 and a CD4 count <350 cells/mm<sup>3</sup> were more likely to have neurosyphilis. Therefore, most investigators recommend CSF examination for all HIV-infected patients with syphilis when serum RPR >1:32 or CD4 count <350 cells/mm<sup>3</sup> regardless of stage of syphilis. Following treatment the response of CSF parameters closely parallels that of decline in serum nontreponemal tests.<sup>35</sup> Therefore repeated CSF examination is not recommended unless RPR serum antibody levels remains ≥1:32. CSF VDRL is relatively insensitive (50%) for predicting neurosyphilis. FTA-ABS test has 100% sensitivity in ruling out neurosyphilis<sup>34</sup> and should be performed as part of the evaluation. However a positive test is not beneficial in diagnosing neurosyphilis. Therefore, any CSF abnormality, including pleocytosis >20 lymphocytes/mL or elevated protein levels should be considered diagnostic in the presence of reactive serum serology.

### Screening and Reporting

Serological screening is critical in diagnosing syphilis. Most guidelines recommend HIV-infected patients to be screened for syphilis at least once per year and for patients with continued high-risk behavior to be screened every 3 months.

Serologic test results for the majority of HIV-infected patients with syphilis are consistent with those seen in non-HIV-infected patients. However, seroreactivity may be delayed or absent,<sup>25</sup> and false-positive nontreponemal antibody tests (RPR/VDRL) has also been seen in HIV-infected patients. In one study, 4% of HIV-

infected patients tested had false-positive RPR.<sup>29</sup> Nontreponemal antibody levels may also decline more slowly after treatment than in HIV-non-infected patients.<sup>30–32</sup> Higher mean serum nontreponemal antibody levels are also reported<sup>34</sup> and prozone reaction occurs more commonly in HIV-infected patients.<sup>33</sup> No correlation has been found between serologic response to therapy and CD4 count.<sup>34</sup> In clinically suspicious cases with negative serological test, alternative tests such as biopsy of lesions or darkground microscopy could be helpful.

### Treatment and Follow-up (Table 84.1)

Due to lack of consistent data on either the frequency of failure or of progression to neurosyphilis and other complications, treatment for syphilis in HIV infected patients should be the same as non-HIV infected patients.<sup>36</sup> Treatment should be appropriate for the stage of the infection. The treatment of choice for all stages of syphilis is penicillin, which must be administered parenterally.<sup>37,39</sup> Azithromycin given as a single 2 g dose appeared effective in treating early syphilis<sup>40,41</sup> but studies have shown that *T. pallidum* develops resistance to this drug.<sup>42</sup> Benzathine penicillin does not reach effective levels against *T. pallidum* in the CSF, and relapses of syphilis with neurosyphilis are common in immunocompromised patients who were treated with a single dose of benzathine penicillin.<sup>16</sup>

Partners of patients with syphilis, regardless of whether they are coinfecting with HIV, should be examined and prophylactically

**Table 84.1** Syphilis Treatment

Treatment of early Syphilis
<ol style="list-style-type: none"> <li>1. Benzathine penicillin G 2.4 MU/IM single dose</li> <li>2. Procaine penicillin G 600,000 units/IM daily for 10 days</li> </ol>
Alternative regimen
<ol style="list-style-type: none"> <li>1. Doxycycline 100 mg/PO – bid for 14 days</li> <li>2. Azithromycin 2 g/PO stat</li> <li>3. Erythromycin 500 mg/PO qds for 14 days</li> <li>4. Ceftriaxone 500 mg/IM daily for 10 days</li> <li>5. Amoxicillin 500 mg/PO qds plus Probenecid 500 mg qds for 14 days</li> </ol>
Treatment of late latent, cardiovascular, and gummatous syphilis
<ol style="list-style-type: none"> <li>1. Benzathine penicillin G 2.4 MU/IM weekly for 2 weeks (3 doses)</li> <li>2. Procaine penicillin G 600,000 units/IM daily for 17 days</li> </ol>
Alternative regimen
<ol style="list-style-type: none"> <li>1. Doxycycline 100 mg/PO – bid for 28 days</li> <li>2. Amoxicillin 2 g/PO tid plus Probenecid 500 mg qds for 14 days</li> </ol>
Treatment of neurosyphilis including neurological and ophthalmic involvement in early syphilis
<ol style="list-style-type: none"> <li>1. Procaine Penicillin G 1.8–2.4 MU/IM daily plus Probenecid 500 mg qds for 17 days</li> <li>2. Benzylpenicillin 18 – 24 MU daily, given as 3–4 MU/IM every 4 hrs for 17 days</li> </ol>
Alternative regimen
<ol style="list-style-type: none"> <li>1. Doxycycline 200 mg/PO – bid for 28 days</li> <li>2. Amoxicillin 2 g/PO tid plus Probenecid 500 mg qds for 28 days</li> <li>3. Ceftriaxone 2 g IM or IV for 10–14 days</li> </ol>

Adapted from BASHH Clinical Effectiveness Group guidelines, May 2009.



treated with single dose benzathine penicillin G 2.4 million units IM. Treatment of partners will depend on the stage of the disease. Sexual transmission of *T. pallidum* occurs only when mucocutaneous syphilitic lesions are present. Since such lesions are uncommon after the first year of infection sexual partners beyond 1 year will not require treatment. For primary syphilis all partners for a period of 3 months plus duration of symptoms should be treated. Partners for 6 months plus duration of symptoms for secondary syphilis and 1 year for early latent syphilis should be treated.

## HERPES SIMPLEX VIRUSES

Herpes simplex virus (HSV) is the etiologic agent of genital herpes. Two serotypes, HSV-1 or HSV-2, are isolated from lesions caused by genital herpes. Classically genital herpes is caused by HSV-2, and orolabial herpes is caused by HSV-1. However, each serotype can cause disease in either location and increasingly HSV-1 has been isolated from genital lesions.<sup>43</sup> Majority of recurrent herpes outbreaks are caused by HSV-2. Serologic studies have documented HSV seropositivity in the overwhelming majority of HIV-infected patients (> 95% in some series).<sup>44,45</sup> A meta-analysis of 19 prospective observational studies reported that infection with HSV-2 increased risk of HIV acquisition 2.7-fold in men and 4.4-fold in women.<sup>46</sup>

HSV-2 infection increases the infectivity of HIV-infected persons by increasing the frequency and quantity of HIV shedding from genital mucosa even in asymptomatic infection. In HIV-uninfected persons the break in the epithelium caused by HSV increases the acquisition of HIV and increases the host susceptibility to HIV infection by upregulating the mucosal immune activity.<sup>47</sup>

## Pathogenesis

Laboratory studies have provided supportive evidence that HSV may be an important cofactor for HIV expression and transmission. In tissues coinfecting with HSV-1, HIV virions appear to be able to infect keratinocytes that lack CD4 receptors and are not usually vulnerable to HIV infection.<sup>48</sup> The HSV regulatory proteins ICP0 and ICP4 (infected cell protein no. 0 and 4) can upregulate the rate of HIV replication *in vitro*.<sup>49</sup> ICP0 and ICP4 transactivate the long terminal repeat (LTR) of HIV-1 and both ICP0 and ICP27 can upregulate HIV expression in CD4+ lymphoid cells. The transactivating protein of HSV, *Vp16*, acts synergistically with the HIV-1 Tat protein to increase HIV transcription from HIV-1 LTR.<sup>50</sup> Herpetic lesions are associated with infiltration of activated CD4 bearing lymphocytes, which may result in increased expression of HIV on mucosal surfaces. The rate of subclinical shedding of HSV is significantly increased in patients infected with HIV. The most common site of shedding is the perianal area. A CD4+ T-cell count <200/mm<sup>3</sup> has been associated with increased subclinical shedding of HSV in men with HIV infection. In a cross sectional study, HSV was isolated in 13% of HIV positive women as compared with only 3.6% of

HIV-seronegative women.<sup>51</sup> Severe episodes of anogenital herpes may be the first clinical signs of immunosuppression.<sup>52</sup> The chronic immunodeficiency brought upon by HIV puts patients at increased risk of HSV reactivation. Studies have demonstrated that acute or reactivated HSV infection may stimulate HIV replication.<sup>53</sup> HIV RNA levels in plasma significantly increased in patients with active herpes lesions. Ioannidis et al.<sup>54</sup> reported that long-term suppressive therapy with acyclovir may prolong survival in AIDS patients with history of severe HSV infections.

## Clinical Presentation

Anogenital disease caused by HSV in HIV-infected patients may vary from that in the non-HIV-infected populations in severity of initial infection or severity and frequency of recurrent infection. Increasingly acyclovir resistance is also encountered in the HIV-infected population. But majority HIV-infected patients with genital herpes present similarly to those in non-HIV-infected patients.

In advanced HIV disease, the lesions could be large, often hemorrhagic, deep, with raised margins simulating donovanosis, syphilis or giant chancroid. A small fraction has chronic persistent mucocutaneous ulceration, often involving large areas of skin in perianal, scrotal, and penile regions. Other atypical lesions seen are hyperkeratotic verrucous lesions and vegetating plaques. The verrucous lesions may closely mimic condyloma accuminata or verrucous carcinoma. Lesions of herpes simplex may acquire a zosteriform appearance.<sup>50</sup> Few patients present with an erythema multiforme like eruption. Ulcers may be coinfecting with other pathogens. Rarely patients with CD4 counts <100 cells/mm<sup>3</sup> may develop disseminated infection characterized by scattered, discrete, eroded, or crusted erythematous papules or papulovesicles. HSV is a common cause of proctitis in HIV-infected men who have sex with men (30% in some series). HSV associated encephalitis has also been reported.<sup>55</sup> Lesions caused by resistant virus may be atypical, more severe, larger, and slower to heal. Lesions of HSV presenting for longer than a month or the occurrence of HSV related pneumonitis, bronchitis or esophagitis in persons with HIV are considered AIDS defining.<sup>56</sup>

The immune response plays an important role in driving HSV into its initial latent state and in maintaining HSV latency.<sup>55</sup> The chronic immunodeficiency in HIV-infected patients increases risk for HSV reactivation and more frequent recurrences occur when CD4 counts is decreased to <100 cells/mm<sup>3</sup>.<sup>57</sup>

## Acyclovir-Resistant HSV

Acyclovir-resistant HSV occurs frequently in HIV infected and other immunocompromised patients. Risk factors for acyclovir resistance include a CD4+ cell count of less than 50/L and herpetic lesions of long duration.<sup>50</sup> In a study done by Safrin et al.<sup>58</sup> the median CD4+ cell count was 24 in 25 HIV-positive patients with acyclovir-resistant HSV. Acyclovir-resistant HSV should be suspected when HSV culture positive lesions persist despite adequate serum concentrations (>2 mcg/mL) of acyclovir.

Most resistant viral isolates are thymidine kinase (TK) deficient and are therefore resistant to acyclovir, valacyclovir, famciclovir, penciclovir, and ganciclovir. If suspected drug susceptibility testing could be carried out. Foscarnet an antiviral agent used to treat acyclovir-resistant HSV inhibits HSV specific DNA polymerase and does not require viral thymidine kinase for phosphorylation. It was observed that with discontinuation of acyclovir and initiation of treatment with foscarnet, a new isolate was recovered, characterized by loss of the acyclovir resistant trait and production of a functional thymidine-kinase enzyme.<sup>59</sup>

## Diagnosis

Diagnostic methods for genital herpes in HIV-infected patients are the same as those for non-HIV-infected patients. Diagnosis of typical genital herpes is usually made through clinical examination. HSV antigen detection including PCR, culture, Tzanck smear and biopsy are useful diagnostic tools. The culture in HSV detection is limited as the sensitivity decreases with the duration of the lesion. All atypical lesions should be confirmed by one of the diagnostic tests. Coinfection with another pathogen, such as syphilis, should be considered in atypical presentations. Serologic testing is of limited value in HIV-infected patients because most series show that the overwhelming majority of HIV-infected patients have antibody to HSV-1 and -2.

## Treatment

Acyclovir, valacyclovir, or famciclovir can be used to treat HSV. Possibility of antiviral resistance should consider in addition to nonadherence and poor absorption if herpetic lesions fail to heal with standard antiviral therapy. Intravenous therapy is necessary for severe mucocutaneous progressive disease, visceral involvement (e.g., oesophageal or hepatic), or antiviral resistance.

### Primary outbreak with uncomplicated presentation

- Acyclovir 400 mg PO tid
- or*
- Famciclovir 250 mg PO tid or 500 mg bid
- or*
- Valacyclovir 1g PO bid

### Reactivation and Chronic Suppressive Therapy

HSV-2 reactivation and viral HSV shedding has been shown to be higher in HIV coinfecting patients than in those who are seropositive for HSV alone,<sup>47,60</sup> indicating the increased risk of HSV transmission by HIV/HSV coinfecting patients.<sup>61</sup> Suppressive anti-HSV therapy has been shown to decrease frequency of recurrences and decrease but does not eliminate, viral HSV shedding and infectivity.<sup>62,63</sup> HSV reactivation is also associated with increased HIV RNA levels<sup>64</sup> and daily HSV antiviral therapy decreases HIV RNA levels to baseline in patients not receiving HAART.<sup>60,64</sup> This has resulted in the use of HSV suppressive therapy to be considered in HIV-infected patients who are not receiving effective ARV therapy.<sup>65</sup> Although

several studies have shown that acyclovir or valacyclovir reduce plasma and genital levels of HIV-1 in HSV-coinfecting patients,<sup>66</sup> two large studies of daily suppressive acyclovir therapy in HIV-uninfected adults among heterosexuals in Africa and MSM in Peru and the United States did not show a reduction in risk of HIV acquisition.<sup>67,68</sup>

### Chronic suppression

- Acyclovir 400–800 mg PO bid or tid
- or*
- Famciclovir 500 mg PO qd or bid
- or*
- Valacyclovir 1 g PO qd

### Treatment Options for Resistant HSV

An algorithm for treatment of ACV resistant HSV was developed at a round table symposium held in March 1993 by the CDC. This suggests:

- Increase the dose of oral acyclovir to 800 mg 5 times a day if new lesions continue to form after 3–5 days of treatment with standard dose.
- If there is no response after 5–7 days and lesions are accessible, the panel recommends addition of topical trifluridine every 8 hours until healing is complete. If lesions are not accessible, IV foscarnet 60 mg/kg twice a day or 40 mg/kg thrice a day until complete healing should be given.
- Foscarnet resistance has been reported and this may make cidofovir the most viable option.<sup>69</sup>
- Cidofovir—topical cidofovir gel 1%, applied to the lesions once daily for 5 days also might be effective.<sup>70</sup>
- Cidofovir 5 mg/kg IV q 2 weeks (limited experience).
- Immunotherapy—with interleukins.
- The use of topical imiquimod is still experimental.

## CHANCROID

Genital ulcers associated with chancroid potentiate the transmission of HIV. CD4 cells are plentiful in these ulcers and HIV can be isolated from HIV coinfecting chancroid ulcers. According to Cameron et al.,<sup>71</sup> men with chancroid are almost 5 times more likely to acquire HIV than those without GUD. HIV induced immunosuppression increases the clinical severity of *H. ducreyi* infection. The comparison of HIV seronegative with seropositive patients with chancroid has shown that seropositive patients have an increased number of genital ulcers than their seronegative counterparts.<sup>72</sup> Alternatively, HIV induced immunosuppression may reactivate genital herpes<sup>73</sup> and the coinfection of HSV with chancroid may explain the increased number of ulcers in such patients. Cases of chancroid with involvement of extragenital sites like digits and legs in association with the penile lesions have also been documented.<sup>74</sup> In advanced HIV disease, patients can present with complications like phimosis, phagedena, giant, multiple and destructive ulcers, which can be mistaken for donovanosis. HIV infection retards

the immune response of lymphocytes to *H. ducreyi* and delays the healing process. Delayed healing of genital ulcers of various etiologies has been reported in HIV-infected patients.<sup>74,75</sup> Delayed healing explains why the recommended single dose therapy with quinolones, ceftriaxone, and azithromycin has high failure rates in HIV-infected patients with chancroid.<sup>76</sup> Current CDC recommendations for treatment of chancroid in HIV-infected patient are the same as those for immunocompetent patients, though patients may require a longer duration of therapy with close follow-up.

### DONOVANOSIS

Donovanosis, being a genital ulcer disease, facilitates transmission of HIV. A few patients of coexisting donovanosis and HIV have been reported from South Africa and Brazil. There are very few reports about the altered clinical manifestations of donovanosis associated with HIV. Jamkhedkar et al.<sup>77</sup> compared the clinical features and response to treatment in genital lesions of donovanosis in both HIV seropositive and seronegative patients. They concluded that although genital ulcers at recruitment were not significantly large among HIV seropositives they took a longer time to completely heal (25.7 vs 16.8 days) and tended to produce greater tissue destruction. Increased incidence of squamous cell carcinoma has been reported in HIV seropositive young patients with donovanosis.<sup>78</sup> Etiological diagnosis is essential because genital ulcers due to HSV or syphilis may simulate donovanosis. The causative organism is difficult to culture and diagnosis requires visualization of dark-staining donovan bodies on tissue crush preparation or biopsy. Though treatment with erythromycin 500 mg 4 times a day for 14 days is quite effective treatment may need to be modified in patients with significant immunosuppression. In India, HIV-positive patients with donovanosis had a higher failure rate to first-line antibiotic therapy.<sup>79</sup> In Brazil, two AIDS patients with donovanosis failed to respond to conventional treatment with combinations of co-trimoxazole, tetracycline, and thiamphenicol. The role of oral azithromycin in the management of donovanosis in HIV-positive patients needs to be evaluated. CDC recommends injection gentamicin 1 mg/kg every 8 hours for such patients.<sup>56</sup> However, among HIV-seropositive pregnant women without significant immunosuppression, the clinical presentation and response to treatment in donovanosis appeared to be unaltered. In those patients, who do not respond, a biopsy is necessary to rule out malignancy.

### LYMPHOGRANULOMA VENEREUM (LGV)

Lymphogranuloma venereum (LGV) is a sexually transmitted infection (STI) caused by unique serovars of *Chlamydia trachomatis* (L1, L2, L3). No current evidence exists to support a difference in acquisition, natural history, or response to therapy of LGV in the setting of HIV coinfection. One retrospective study has shown that HIV appears to have no adverse effect on clinical features of LGV.<sup>80</sup> LGV should be considered in the

differential diagnosis of GUD, inguinal lymphadenopathy, or proctocolitis, especially in men who have sex with men. The CDC currently recommends that HIV care providers be alert for LGV in patients with rectal symptoms or proctitis. LGV proctitis can present not only with symptoms of classic sexually transmitted proctitis such as, bloody or purulent rectal discharge, tenesmus, pain on defecation but can also present in a more indolent fashion. Several diagnostic challenges can further confound one's ability to diagnose LGV. Diagnosis is based on clinical suspicion, epidemiologic information and the exclusion of other etiologies along with testing for *C. trachomatis* similar to non-HIV-infected patient. CDC recommends the same line of treatment for LGV as in HIV-negative patients; however, HIV-positive patients may require a longer course. Partners of patients with LGV who had sexual contact with the patient within 60 days prior to symptom onset should be examined and treated.

### NEISSERIA GONORRHOEAE AND CHLAMYDIA TRACHOMATIS

The incidence of concomitant gonorrhea and chlamydia is high among HIV-infected patients. Several studies have shown that infection with *N. gonorrhoeae* and/or *C. trachomatis* may increase both the risk of transmission and acquisition of HIV.<sup>81-83</sup> There are many reports showing statistically significant association of gonorrhea with HIV seroconversion<sup>4-8</sup> with risk estimates ranging from 3 to 5. In a study from Baltimore, the risk for female to male HIV transmission was doubled in gonorrhea patients.<sup>5</sup> All HIV-infected patients with ongoing high-risk sexual behaviors should be screened for gonorrhea and chlamydia at baseline and at least annually. There have been no formal studies evaluating differences in clinical presentation, diagnosis, or response to treatment of gonococcal or chlamydial infection in HIV-infected patients. There have been no reports of atypical presentations or failure of standard therapy in HIV-infected patients. Diagnostic tests and treatment recommendations are identical to those in non-HIV-infected patients.<sup>84</sup> There are also few anecdotal reports of increased recurrence of gonorrhea in HIV-infected individuals.<sup>85</sup>

### VAGINAL INFECTIONS IN HIV-INFECTED WOMEN

#### Trichomonas Vaginalis

Genital tract infection with *Trichomonas vaginalis* (TV) increases HIV shedding in the vaginal secretions of infected women and in the semen of infected men. Therefore, trichomoniasis plays an important role in HIV transmission. A nearly three-fold increase risk of HIV due to trichomoniasis was found in a recent study from sub-Saharan Africa.<sup>86</sup> In addition, successful treatment of trichomoniasis in HIV-infected women has been shown to reduce genital HIV shedding.<sup>87</sup> Clinical presentation, diagnosis, and treatment in HIV infected patient are identical to those in non-HIV-infected patients.



## Bacterial Vaginosis

Bacterial vaginosis, one of the commonest causes of vaginal discharge increases women's vulnerability to HIV infection.<sup>88</sup> An increased genital shedding of HIV has been observed in HIV-positive women with bacterial vaginosis. This increase in genital HIV shedding could be due to bacterial vaginosis caused changes in the genital immune cell population, most importantly an increase in CD4 cells with the CCR5 co-receptor, which are targets for HIV and could increase local HIV replication.<sup>89</sup> There are no difference in the clinical presentation, diagnosis, and treatment of bacterial vaginosis in HIV infected and non-HIV-infected patients.

## Genital Candidiasis

Vaginal candidiasis is increasingly reported in women with HIV.<sup>90</sup> The degree of immunosuppression plays an important role in HIV associated recurrent vulvovaginal candidiasis. Although majority of infection will response to intravaginal antifungal agents, with advance immunosuppression systemic antifungal therapy would be required.<sup>90</sup> Long term prophylactic therapy may be required in patients who are not on HAART.

## Molluscum Contagiosum (MC)

Two types of molluscum contagiosum viruses (MCV) MCV 1 and 2 have been identified. MCV 2 is common in adult men and patients with HIV infection.<sup>91</sup> 10–30% of patients with symptomatic HIV disease or AIDS have MC.<sup>92</sup> The prevalence and the severity of the disease increase with advancing immunodeficiency. Up to one third of patients with CD4+ T-cell counts of 100/mm<sup>3</sup> or lower will present with lesions.<sup>93</sup> Often molluscum in AIDS patients reflects the reactivation of latent MCV.<sup>94</sup> The individual lesions of MC may be quite large with a diameter of 10 mm or more (giant MC). The appearance of multiple lesions is more common than solitary papules and plaques. Sometimes the lesions may resemble comedones, abscesses, furuncles, condylomata, basal cell carcinomas, ecthyma, and cutaneous horns.<sup>95–98</sup> Lesions of MC are usually distributed over the face, including eyelids and ears, neck and in intertriginous areas like axilla, groin, or buttocks. In homosexual men, the lesions are often seen in the anogenital area, possibly related to sexual transmission. These lesions may have a varied morphology ranging from fine papular lesions to verrucous hypertrophic lesions and polypoidal masses. It is important to differentiate such lesions from keratoacanthoma, cryptococcosis, histoplasmosis, penicilliosis, and coccidioidomycosis, which are also common in HIV infected patients. Histological sections from HIV infected patients may show areas of acanthosis, hyperkeratosis, and nuclear atypia, which is hardly ever seen in HIV-seronegative individuals. Viral structures consistent with MC are present in the clinically uninvolved epidermis adjacent to the lesions of MC in some HIV infected patients. This may explain the large number of lesions seen in these patients and the difficulty in controlling the spread

and recurrences of MC lesions.<sup>99</sup> Treatment in HIV-seropositive patients is not very effective as new lesions frequently erupt.<sup>100</sup> Intralesional interferon alpha results in shrinkage of treated lesions but has no benefit on surrounding lesions.<sup>101</sup> Imiquimod deserves consideration.<sup>102</sup> Cidofovir, either by topical or intravenous route, may be effective in recalcitrant mollusca.<sup>103</sup> Clearance of MC is seen with HAART as the immunity improves. If HAART is commenced with low CD4 count (below 200/mm<sup>3</sup>) an increase in MC may be seen as part of immune reconstitution syndrome.

## GENITAL WARTS

Human papillomaviruses (HPV) are a large group of viruses that are capable of infecting squamous epithelia. About 30 different HPV types have a predilection for the anogenital tract and may cause asymptomatic infection, condylomata acuminata, squamous intraepithelial neoplasia, and rarely other anogenital carcinomas including cervical neoplasia in women. Patients can be infected with more than one HPV type and can be at risk for both dysplasia and benign disease. The prevalence of HPV in HIV-infected patients varies over time with the degree of immunosuppression.<sup>104</sup> HIV facilitates either the activation of recently acquired HPV infection or the reactivation of latent infection, or both.

HPV types 16 and 18 are responsible for the development of approximately 70% of cervical and anal dysplasia and cancer. HPV types 6 and 11 account for approximately 90% of benign genital warts.<sup>105</sup>

The presentation of HPV in HIV-positive patients ranges from condylomata acuminata (genital warts) to carcinoma. Various studies have shown an increased incidence of anogenital warts in HIV-seropositive individuals.<sup>106</sup> Kiviat et al.<sup>107</sup> demonstrated that HIV-seropositive men are 3.1 times more likely to be positive for HPV DNA by PCR than seronegative men and that the former often have infection with multiple subtypes of HPV compared with the latter (44% vs 23%). Critchlow et al.<sup>108</sup> also demonstrated that HIV seropositive asymptomatic men were 4.1 times more likely to have anal HPV DNA detected by PCR than seronegative men, and seropositive men with other constitutional, neurological or infectious diseases associated with HIV were 10.9 times more likely to have HPV detected from the anal canal.

The differentiation properties of perianal epithelium are different from epithelium of the penile shaft. These differences determine the expression pattern of HPV as the perianal epithelium shifts the HPV expression to the early genes. HIV infection might also activate HPV early genes in a tissue specific manner, favoring the perianal epithelium. Consequently perineum may mount lower immune response against HPV infections since it is more depleted in immune presenting cells, such as Langerhans cells, CD4+ T cells and macrophages. This local immunodeficiency may account for the higher rate of HPV occurrence in the perianal area than on the penile shaft.<sup>109</sup> HIV infected patients also have higher rates of cervical, anal, and other genital cancers. It is possible that HIV acts directly on

HPV. *In vitro* studies have shown that intracellular HIV-1 Tat mRNA can transactivate HPV type 16 E6 and E7, an action that is important in the development of squamous cell cancers. *In vitro* studies have also shown that extracellular HIV-1 Tat protein can enter HPV infected cells and upregulate HPV type 16 E6 and E7, and it also enhances E2 dependent HPV type 16 transcription. It is possible that extracellular Tat migrates from Langerhans cells or other HIV infected mononuclear cells to HPV infected epithelial cells and upregulate HPV.<sup>110</sup> Women with HIV infection appear to be at increased risk for HPV and related cervical intraepithelial neoplasia (CIN). Odd ratio for association between HIV and CIN has ranged from 10% to 14.7%.<sup>111</sup> The presence of HPV DNA, extent of disease and potential for the malignant transformation also appear to correlate with the degree of immunosuppression. Individuals with CD4+ cell counts less than 200/mm<sup>3</sup> are at the greatest risk.<sup>112</sup> Cervical cancer in an HIV-seropositive patient is an AIDS-defining illness.<sup>113</sup> Anal cancer is currently the fourth most common cancer among HIV-positive men,<sup>114</sup> and is about 7 times more common in homosexual men with HIV than those who are HIV seronegative and 40 times more common in homosexual men with AIDS.<sup>115</sup>

HIV infected patients have multiple lesions and even diffuse involvement of the anogenital areas.<sup>104</sup> They develop very large genital warts. On rare occasions, these become locally invasive and destructive (giant condylomas or Buschke-Lowenstein tumor). Although these tumors, are non metastasising,<sup>107</sup> they carry a significant risk of transformation into squamous cell carcinoma. CIN vulval (VIN) and anal intraepithelial neoplasia (AIN) have all been reported to occur more frequently in HIV-infected patients. Increased severity of HPV disease is seen with increased immunosuppression. They are more resistant to treatment, more likely to recur and develop anal and CIN with increased relative risk of developing in situ or invasive genital cancers.<sup>114–119</sup>

Diagnosis of external condylomata acuminata is usually made on clinical grounds. HPV should be considered in the differential diagnosis of anogenital symptoms, such as itching, bleeding, pain, or spotting after sexual intercourse. Patients with abnormal anogenital physical findings, such as, hypopigmented or hyperpigmented warty lesions, lesions that bleed, or any other lesions of uncertain etiology should be biopsied. Clinicians should maintain a low threshold to obtain biopsy of atypical lesions in HIV infected patients to excluded dysplastic changes or squamous cell cancer.

Examination of the anogenital area, including the vulva and vagina in women, should be made to assess for HPV lesions at baseline and as part of the annual physical examination in HIV infected patients. Cervical Pap smear should be carried out in all HIV-infected women at baseline, 6 months after baseline and then repeated annually, as long as results are normal. Anal cytology helps in the detection of precancerous dysplastic lesions or treatable early invasive disease. Pap smear of the anal canal are simple to perform and clinically effective<sup>120,121</sup> with comparable sensitivity and specificity to cervical cytology.<sup>122</sup> Similar to cervical

tissue, the anal epithelium at the dentate line has a transformation zone between squamous and columnar epithelia. This transition zone is subject to infection with and neoplastic transformation by HPV. Precancerous lesions of the anal squamous epithelium can develop and are classified according to identical Bethesda criteria and nomenclature developed for grading cervical lesions.<sup>123</sup> Anal cytology should be obtained at baseline and annually in HIV-infected men who have sex with men, patients with a history of anogenital condylomas and in women with abnormal cervical, vaginal, or vulval histology. Colposcopy should be performed in all HIV-infected women with any abnormal cervical cytology and anoscopy performed in all HIV-infected patients with abnormal anal cytology. Follow-up and treatment will depend on the abnormality. The use of HPV DNA testing can be a useful adjunct to Pap smears in non-HIV-infected women but it is not recommended in HIV-infected patients.

## Treatment

Treatment of genital wart in HIV-infected patients does not defer from those used in non-HIV-infected patients. However, HIV-infected patients have a much higher rate of recurrences.<sup>106</sup> Cryotherapy, podophyllotoxin, interferon, imiquimod, cidofovir gel, trichloroacetic acid (TCA), and bichloroacetic acid (BCA) have all been studied in small numbers of HIV-infected patients with mixed results. Some clinicians advocate treatment by excision and electrodesiccation because of the poor response and frequent recurrences after topical treatments.<sup>124</sup> Poor clearance rates are reported after therapy in HIV-infected patients with advanced immunosuppression. More than one method of treatment or longer duration of treatment is often needed. HPV vaccine should be offered to HIV-infected women between the ages of 9 and 26 years. Most of the data regarding HPV vaccine safety and efficacy are derived from studies in non-HIV-infected females. Studies are currently underway to provide more extensive data regarding the safety and efficacy of the vaccine in the HIV-infected population. HIV-infected women may have reduced antibody response to the immunization. Women who have been vaccinated with HPV vaccine should continue cytological surveillance as described above. There is currently are no recommendations to vaccinate males against HPV.

## HUMAN HERPES VIRUS-8

Human herpes virus-8 (HHV-8) was originally identified in Kaposi's sarcoma (KS) tissue from AIDS patients. HHV-8 is also associated with a rare type of non-Hodgkin's lymphoma (NHL), termed primary effusion lymphoma, and with the plasma cell variant of Castleman's disease. Furthermore, patients with HIV associated KS are at a significantly greater risk for the development of NHL than their unaffected counterparts. Although the biology of HHV-8 is not entirely understood, it appears to be a sexually transmitted infection in Western Europe and USA.

Most cases of AIDS associated KS have appeared in men who participated in homosexual activities or had a history of STIs.

Those persons who acquired HIV nonsexually (hemophiliacs or intravenous drugs abuser) have much lower rates of KS than those who contracted HIV from homosexual or bisexual contacts.<sup>125</sup>

Many studies have focused on shedding of HHV-8 in semen with variable results. Patients with KS appear to consistently shed HHV-8 virions in their oral secretions. Variety of lesions like patches, plaques, papules, nodules, and ulcers may appear anywhere on the skin or mucous membranes. Visceral involvement in KS, commonly affects the gastrointestinal tract, lymph nodes, and lungs associated with significant morbidity and mortality. In era of HAART, KS is seen much less commonly, suggesting that the development or resolution of KS is linked to immune system control of HHV-8.

### SCABIES

The clinical features of scabies in the HIV-positive patients are often determined by the degree of immunosuppression. As the immunity decreases ( $CD4^+$  cells  $<200/mm^3$ ), the more contagious and fulminant forms of scabies become apparent.<sup>126,127</sup> The unusual forms of scabies in HIV-seropositive patients can be divided into two overlapping categories, namely, papular and crusted (Norwegian or hyperkeratotic) forms. The papular forms are characterized by severely pruritic, generalized papules, topped by scabetic burrows, which may be scaly. The crusted forms are characterized by thick, friable, white-gray plaques, which may also be diffuse, but are commonly localized to scalp, face, back, buttocks, nails, and feet. The plaques are often associated with mild to severe fissuring. As the lesions become crusted, they tend to become less pruritic. Both forms may coexist. Scabies should be considered in any HIV-positive patient presenting with an atypical or pruritic rash. These patients may harbor thousands of scabies mites and they are highly contagious, as the shed crusts are loaded with mites. The crust can serve as food supply and protection: sustaining the mites for up to a week.<sup>128</sup> CDC treatment recommendations for treatment of scabies in HIV-infected patients are the same as for HIV-negative patients.

### HEPATITIS B VIRUS (HBV)

Majority of studies have shown that there is no increased risk for rapid development of AIDS or decline in  $CD4^+$  counts in hepatitis B virus (HBV) positive patients.<sup>129</sup> However, HIV infected individuals are at increased risk for acquisition of HBV and during acute HBV infection HIV-seropositive patients tend to develop more severe illness. They are also at increased risk for chronic HBV infection. Liver function profile of chronic carriers of HBV is less abnormal when they are coinfecting with HIV, perhaps reflecting less severe hepatic inflammation. Asymptomatic reactivation or reinfection with HBV appears to be relatively common among HIV infected persons, especially if they have marked immunosuppression. It is also observed that the response of HIV infected persons to vaccination against HBV is impaired. HEPATITIS C VIRUS (HCV) The rates of sexual transmission of hepatitis C virus (HCV) are

low among heterosexuals. Outbreaks of sexually acquired HCV infection have been reported, almost exclusively in MSM who reported sexual practices involving exposure to blood or even minimal trauma to the rectal mucosa.<sup>130</sup> Acute HCV infection should be considered in the differential diagnosis of transaminitis. HCV infection can hasten the progression of HIV and HIV infection can impair the response to treatment of HCV.

### CYTOMEGALOVIRUS (CMV)

Cytomegalovirus infection is common in AIDS. Patients with multiple partners are more likely to be infected with multiple strains of the virus. Several GI syndromes have been associated with CMV, including esophageal ulcers, esophagitis, gastritis, isolated intestinal ulcers, terminal ileitis, intestinal perforation, focal or diffuse colitis, hepatitis, pancreatitis, sclerosing cholangitis, and unexplained wasting. The key histopathologic feature is intranuclear and intracytoplasmic inclusions. Ganciclovir and foscarnet are effective.<sup>131</sup>

### SEXUALLY TRANSMITTED GASTROINTESTINAL PATHOGENS

Sexually transmitted gastrointestinal syndromes such as proctitis, proctocolitis, and enteritis occur in HIV infected patients similar to HIV-negative individuals. When outbreaks of gastrointestinal illness occur among men who have sex with men, sexual transmission should be considered. The gastrointestinal tract appears to be a major target organ in HIV infected patients, and all infections have a more aggressive course. Quinn et al.<sup>132</sup> have shown that 63% of HIV seropositive homosexual patients with anorectal diseases had more than one lesion at the time of presentation, and 20% had more than one pathogen identified. A wide variety of anorectal lesions have been described including ulcers, condylomas, fissures, fistula, and abscesses. Anorectal HSV in HIV infected patients tends to develop chronic progressive disease leading to large, destructive perianal ulcers. Rectal gonorrhea increases the risk of HIV acquisition 3-fold.<sup>133</sup>

Proctitis occurs predominantly among persons who participate in receptive anal intercourse. *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, lymphogranuloma venereum (LGV), *Treponema pallidum*, and herpes simplex virus are the most common sexually transmitted pathogens. Proctocolitis is associated with symptoms of proctitis and diarrhea or abdominal cramps. Sexual transmission occurs via oral–anal contact. Causative organisms include *Campylobacter* sp., *Shigella* sp., *Entamoeba histolytica*, and rarely, LGV. CMV or other opportunistic agents might be involved in HIV-infected patients. Enteritis usually results in diarrhea and abdominal cramping without signs of proctitis or proctocolitis. It is also acquired by oral–anal contact. *Giardia lamblia* is the most frequently implicated organism in non-HIV-individuals. Studies evaluating the microbiology of HIV associated gastrointestinal diseases found cryptosporidiosis in 30%, Isospora in 10%, and *E. histolytica*, *G. lamblia*, Salmonella, and CMV in 5–10% of patients.<sup>134,135</sup> Multiple stool examinations might be necessary to diagnose these organisms. Blood culture



is advisable in suspected infectious diarrhea with fever in an HIV-infected patient.

Sexual transmission of enteric pathogens like *Shigella*, *Salmonella*, and *Campylobacter jejuni* is more common in homosexual men with AIDS. Also, the infections are more prolonged with frequent recurrences, bacteremia, and antibiotic resistance. Although there has been no documentation of sexual transmission of *Cryptosporidia*, *Isospora*, and *Microsporidium* which have been detected more frequently in patients with AIDS, this mode of transmission is suspected due to their relative high isolation rate in homosexual than in other categories of patients with HIV. Chronic severe *Isospora* and *Cryptosporidia* infection are associated with CD4+ cell count less than 100/L.<sup>136</sup> *Cryptosporidium* is the most widely recognized enteric pathogen with a worldwide distribution of 10% to 20% in patients with AIDS.<sup>137</sup> *Cryptosporidiosis*, which is usually chronic and protracted, is a cause of wasting syndrome or "slim disease". Protracted disease occurs despite the presence of antibody in stool, suggesting that antibodies do not help much. Patients with *cryptosporidiosis* may present with diffuse small intestinal disease, mild colonic involvement, ileocolitis, isolated ileitis, massive secretory diarrhea, pancreatitis, sclerosing cholangitis, or cholecystitis. *Cryptosporidiosis* can be diagnosed by stool examination or by intestinal aspirate. Treatment with spiramycin and paromomycin are effective. *Isospora belli* is a coccidium closely related to *Cryptosporidium*, with isolation rates ranging from 8% to 20% among African AIDS patients to only 0.2% among American patients with AIDS.<sup>138</sup> Symptoms are similar to *cryptosporidiosis*. Although sulfonamides are effective half of them relapse following treatment.

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# Human Immunodeficiency Virus Infection in Women

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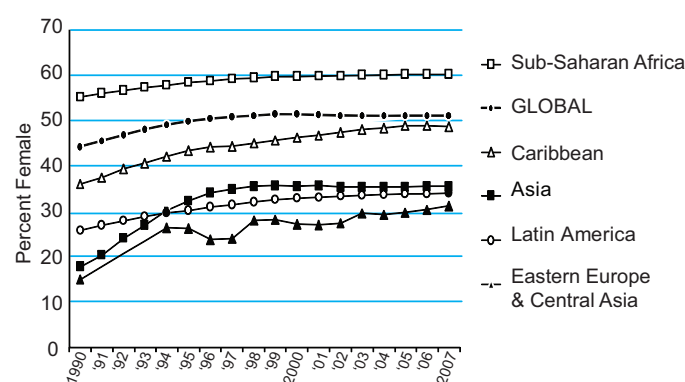
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## Introduction

The human immunodeficiency virus (HIV) pandemic has matured and evolved since the first cases of acquired immunodeficiency syndrome (AIDS) were noted in June 1981 among a cluster of men in Los Angeles, California, who reported having had sex with men.<sup>1</sup> Two distinct species of HIV exist, HIV type 1 (HIV-1) and HIV type 2 (HIV-2); HIV-1 is responsible for most infections globally and it is associated with more rapidly progressive disease than HIV-2 in untreated persons.<sup>2</sup> At the end of 2009 an estimated 33.3 million persons were living with HIV worldwide with heterosexual penile-vaginal intercourse accounting for most transmission of HIV-1.<sup>2</sup> Over time, there has been progressive feminization of the global pandemic with the proportion of affected women increasing steadily worldwide (Fig. 85.1) despite the most recent reported progress in reaching the target set in Millennium Development Goal 6 to halt and begin to reverse the spread of HIV/AIDS by 2015 (Table 85.1).

According to the World Health Organization (WHO), by the end of 2010 over one-half of all HIV infections worldwide

were among women.<sup>3</sup> The distribution of the estimated 18 million infected women is disproportionately concentrated in low-resource countries particularly sub-Saharan Africa (Fig. 85.2). For example, in the 9 most affected countries, all of which are in

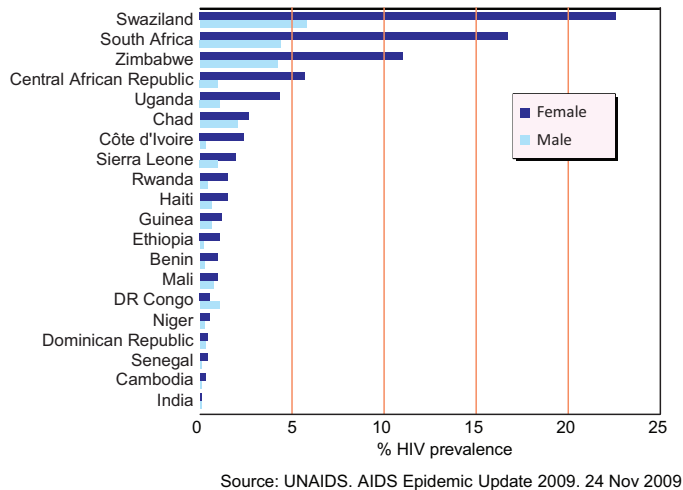


**Fig. 85.1:** HIV infections among women, 1990-2007, by region, per 100 cases. *Source:* UNAIDS. AIDS Epidemic Update 2009. November 24, 2009.

**Table 85.1:** Progress Toward Achieving the HIV/AIDS Related Targets of Millennium Development Goal 6: Combat HIV/AIDS, Malaria and Other Diseases

HIV/AIDS-Related Target	Progress to Date
Have halted by 2015 and begun to reverse the spread of HIV/AIDS	<ul style="list-style-type: none"> <li>Spread of HIV appears to have stabilized in most regions, and more people are surviving longer</li> <li>Many young people still lack the knowledge to protect themselves against HIV</li> <li>Empowering women through AIDS education is possible, as a number of countries have shown</li> <li>In sub-Saharan Africa, knowledge of HIV increases with wealth and among those living in urban areas</li> <li>Disparities are found in condom use by women and men and among those from the richest and poorest households</li> <li>Condom use during high-risk sex is gaining acceptance in some countries and is one facet of effective HIV prevention</li> <li>Mounting evidence shows a link between gender-based violence and HIV</li> <li>Children orphaned by AIDS suffer more than the loss of parents</li> </ul>
Achieve, by 2010, universal access to treatment for HIV/AIDS for all those who need it	<ul style="list-style-type: none"> <li>The rate of new HIV infections continues to outstrip the expansion of treatment</li> <li>Expanded treatment for HIV-positive women also safeguards their newborns</li> </ul>

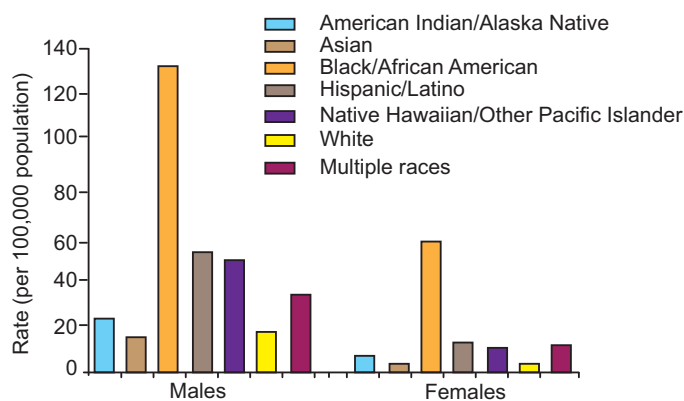
*Source:* United Nations. The Millennium Development Goals Report 2010. United Nations, New York. June 15 2010. Available at: [www.un.org/millenniumgoals/pdf/MDG%20Report%202010%20En%20r15%20-low%20res%2020100615%20-.pdf](http://www.un.org/millenniumgoals/pdf/MDG%20Report%202010%20En%20r15%20-low%20res%2020100615%20-.pdf). Accessed September 30, 2010.



**Fig. 85.2:** Estimated HIV prevalence among females and males in highly affected countries, 2008. *Source:* UNAIDS. AIDS Epidemic Update 2009. November 24, 2009.

sub-Saharan Africa, young women are between 4 and 13 times more likely to be infected with HIV compared with young men<sup>2</sup>. Approximately 4.7 million adults are living with HIV in Asia, 34% of whom are women.<sup>2</sup> The number of women living with HIV and AIDS in Asia varies greatly among different countries. In India, for example, it is estimated that 2.3 million adults are living with HIV of which 38% are women; heterosexual transmission was responsible for 90% of these cases.<sup>2</sup> A similar pattern is noted in other Asia-Pacific countries including Indonesia, Vietnam, and Pakistan.<sup>2</sup>

The overall distribution of HIV infections in high-resource countries, such as the USA, is concentrated in men-who-have-sex with men (MSM).<sup>4</sup> However, in the US, women and adolescent girls account for an increasing proportion of persons living with HIV and AIDS increasing from 7% in 1985 to 27% in 2007<sup>4</sup> (Fig. 85.3). Adolescent girls and young women ages 13 to 24 years



**Fig. 85.3:** Estimated rates of HIV infection among U.S. adults and adolescents, by gender and race/ethnicity 2008–37 states with confidential name-based HIV infection reporting. *Source:* Centers for Disease Control and Prevention. HIV Surveillance Report, 2008; Vol 20.

living with HIV, those from ethnic/racial minorities represent 83% of cases but only 27% of the overall age-matched female population.<sup>5</sup> Although HIV/AIDS is no longer among the 10 leading causes of death in the US, certain subgroups in the population bear a disproportionate burden of the disease. For example, in 2004, HIV was the leading cause of death among black women aged 25–34 years; the third leading cause of death among those aged 35–44 years; and the fourth leading cause of death among Latina women aged 35–44 years.<sup>6</sup>

## Transmission of HIV in Women

Worldwide, over 90% of HIV infections in adolescent females and women are due to heterosexual transmission.<sup>2</sup> However, in higher resource countries injection drug use (IDU) plays a more significant role in acquisition. For example, in the US, in 2008 approximately 20% of infections in women were via IDU.<sup>4</sup> Risk factors for transmission of HIV to women from their male sexual partners are complex and often interrelated and influenced by biological, social, and economic factors. Although commonly perceived to be more efficiently transmitted from women to men than vice versa, this remains an unresolved issue with conflicting outcomes from various studies. This is likely related to multiple factors that may simultaneously influence infectiousness and susceptibility as well as the differing quality of the studies. For example, some of the risk factors examined during these studies relied upon self-reported behaviors that are difficult to validate, adding increased uncertainty to statistical models.<sup>7,8</sup>

Risk factors for heterosexual acquisition of HIV in women have been well-documented. These include presence of genital ulcer disease,<sup>9,10</sup> other sexually transmitted infections in either the woman<sup>11,12</sup> or her partner,<sup>13,14</sup> other non-sexually transmitted genital<sup>15–17</sup> infections and other non-infectious causes of genital irritation or inflammation,<sup>18</sup> the stage of infection,<sup>19,20</sup> the HIV-infected partner's use of antiretrovirals (ART) and viral load,<sup>19,21–23</sup> type of sexual activity,<sup>24,25</sup> and mean age of the woman.<sup>26,27</sup> These risk factors for HIV acquisition are further enhanced by the high prevalence of non-consensual sex,<sup>28,29</sup> failure to use effective physical barrier methods,<sup>30,31</sup> uncircumcised HIV-infected male partner,<sup>32,33</sup> and the known or unknown high-risk behaviors of their partners.

Cohort studies conducted in the US have demonstrated an increased risk of heterosexual transmission to be associated with alcohol use,<sup>34</sup> history of childhood sexual abuse,<sup>35</sup> current domestic abuse,<sup>35</sup> and use of crack-cocaine.<sup>36,37</sup>

## Intimate Partner Violence in HIV/AIDS

High prevalence rates of HIV infection among women globally are inextricably intertwined with the perpetual pandemic of violence against girls and women.<sup>38</sup> This violence manifests itself in the home, the workplace, against sex workers, in conflict settings, and in trafficking of girls and women.<sup>39</sup> The intimate partner may perpetrate physical, sexual, and/or psychological violence (Table 85.2). Worldwide, 10–70% of women report



**Table 85.2:** Forms of Intimate Partner Violence (with Examples)

HIV/AIDS-Related Target	Progress to Date
Have halted by 2015 and begun to reverse the spread of HIV/AIDS	<ul style="list-style-type: none"> <li>• Spread of HIV appears to have stabilized in most regions, and more people are surviving longer</li> <li>• Many young people still lack the knowledge to protect themselves against HIV</li> <li>• Empowering women through AIDS education is possible, as a number of countries have shown</li> <li>• In sub-Saharan Africa, knowledge of HIV increases with wealth and among those living in urban areas</li> <li>• Disparities are found in condom use by women and men and among those from the richest and poorest households</li> <li>• Condom use during high-risk sex is gaining acceptance in some countries and is one facet of effective HIV prevention</li> <li>• Mounting evidence shows a link between gender-based violence and HIV</li> <li>• Children orphaned by AIDS suffer more than the loss of parents</li> </ul>
Achieve, by 2010, universal access to treatment for HIV/AIDS for all those who need it	<ul style="list-style-type: none"> <li>• The rate of new HIV infections continues to outstrip the expansion of treatment</li> <li>• Expanded treatment for HIV-positive women also safeguards their newborns</li> </ul>

Source: World Health Organization. Violence against women. [www.who.int/mediacentre/factsheets/fs239/en/](http://www.who.int/mediacentre/factsheets/fs239/en/). Accessed September 30, 2010.

physical abuse,<sup>40</sup> and 6–45% report sexual violence by an intimate partner at least once during their lives.<sup>28</sup> Furthermore, between 7% and 48% of females aged 10–24 years report that their first sexual encounter was coerced.<sup>41</sup>

Studies from both high- and low-resource countries have demonstrated statistically significant association with HIV acquisition among girls and women reporting intimate partner violence (IPV) compared with those women not reporting IPV.<sup>35,42,43</sup> Several mechanisms have been postulated to account for this observation, including (i) greater biological risk due to trauma of the vaginal, anal, or oral mucosa during coercive sexual contact,<sup>44,45</sup> (ii) increased sexual risk taking as an observed outcome of having experienced childhood sexual abuse, forced sexual initiation during adolescence, or ongoing IPV,<sup>35</sup> (iii) inability or limited ability to negotiate condom use due to a history or fear of IPV,<sup>38,46</sup> and (iv) lack of power or control in a partnership with age disparities, or with an intimate partner with ongoing risky behaviors for HIV acquisition, such as extramarital sexual liaisons or IDU.<sup>47,48</sup> Furthermore, violence or fear of violence should the woman's HIV infection state be discovered and/or revealed may lead to delayed diagnosis and/or treatment.<sup>46</sup>

Additional research is needed to test whether these demonstrated direct and indirect associations are causal. In the meantime, ongoing multi-sectoral approaches aimed at stemming both IPV and HIV/AIDS pandemics among women are in place. These include legal efforts to protect women, enhancing efforts aimed at the empowerment of women, and increasing both public awareness of the problems and providing education to prevent their occurrence.

## Clinical Signs and Symptoms of HIV Infection, AIDS and Associated Conditions in Women

Most manifestations of HIV infection are similar in women and men. Both may have non-specific symptoms in early HIV infection, including low-grade fevers, night sweats, fatigue, and weight loss. ART, as well as prevention and treatment and

prophylaxis of opportunistic infections (OI) appear to be similarly effective in women and men. Some conditions, however, occur with different frequencies in women and men. For example, HIV-infected men are eight times more likely than HIV-infected women to develop Kaposi sarcoma,<sup>49</sup> whereas in some studies, women had higher rates of herpes simplex infections<sup>50</sup> and bacterial pneumonia than men.<sup>51</sup> It is unclear if the differential rate of bacterial pneumonia is due to a gender-specific biological factor or to socio-cultural or socio-economic factors related to access to care as well as HIV-specific prevention and treatment modalities.

Women also suffer gender-specific manifestations of HIV disease, such as vaginal infections, pelvic inflammatory disease (PID), and human papillomavirus (HPV)-related cervical and other lower genital tract dysplasia. Many of the gynecological problems seen in HIV-infected women are the same as those experienced by HIV-uninfected women, with the former often experiencing more frequent or more severe infections, especially with greater immunosuppression. Vulvovaginal candidiasis is more frequent and more persistent and bacterial vaginosis is more persistent.<sup>52–55</sup> Large cohort studies have not shown significant differences in the prevalence of sexually transmitted causes of abnormal vaginal discharge, including gonorrhea, chlamydia, or trichomoniasis.<sup>56,57</sup> Human papillomavirus infections manifesting as either genital warts or cervical and other lower genital tract dysplasia, occur more frequently in HIV-infected women and are more likely to recur after treatment than in uninfected women.<sup>58–63</sup>

Herpes simplex virus (HSV) infections are more prevalent in HIV-infected than non HIV-infected women. Moreover, the frequency and severity of HSV genital ulcers as well as frequency of subclinical shedding are increased by HIV; although this is related to the level of immunosuppression, HIV-HSV co-infected women on ART, still have comparatively more genital ulcers and subclinical HSV shedding.<sup>64,65</sup>

PID appears to be more severe in HIV-infected women than in uninfected women and may be more likely to have tubo-ovarian abscesses or require more prolonged hospitalization,

but overall response to standard management is not affected by HIV status.<sup>66–68</sup> Although menstrual irregularities are often reported by HIV-infected women, data are conflicting as to the role of HIV or HIV-related immunosuppression in menstrual abnormalities<sup>69,70</sup> and there are numerous potential confounding factors, including drug and alcohol use, weight loss, and use of psychotropic medications.<sup>71</sup> Some studies have shown increased likelihood of prolonged amenorrhea and potentially earlier menopause.<sup>72–74</sup>

Idiopathic genital ulcers are a unique manifestation of HIV infection similar to aphthous ulcers.<sup>75</sup> These ulcers are generally seen with profound immunosuppression, and may co-exist with oro-esophageal ulcers or result in genital tract fistula formation. Genital ulcers can also be caused by cytomegalovirus (CMV) in the setting of severe immune compromise.<sup>76</sup> Women with ulcers that are persistent or worsening, have negative testing and do not respond to empiric treatment for more common causes of genital ulceration should have biopsy performed to rule out malignancy and to obtain appropriate immunohistochemical studies.

Finally, although initial studies reported lower levels of steady-state plasma viremia in HIV-1–infected women compared to their male counterparts, they failed to detect sex-associated differences in rates of disease progression. More recently a clinical trial showed that viral decay rates did not differ by sex.<sup>77</sup>

## HIV Diagnosis and Management

Early diagnosis of HIV infection is critical in the management of the HIV-infected woman in order to optimize quality of life, prolong survival, and prevent mother-to-child transmission through informed reproductive choices.<sup>78</sup> Ideally, all women should be encouraged to undergo HIV counseling and testing if they or their sexual partners have engaged in behaviors that put them at risk of infection. In the US, for example, the Centers for Disease Control and Prevention recommends HIV screening for all persons aged 19–64 years at least once as part of routine medical care and targeted screening for those with risk factors who are outside this age range.<sup>79</sup> The American College of Obstetrics and Gynecology recommends annual review of HIV risk factors and rescreening at least annually for women with known risk factors for HIV acquisition.<sup>80</sup> Knowledge of one's sero-status may result in earlier initiation of ART, if indicated, with subsequent immune reconstitution and longer survival and/or modification of sexual behaviors to decrease risk of transmission to uninfected partners.<sup>81,82</sup> Women whose HIV infections are detected early and receive appropriate treatment survive as long as HIV-infected men.<sup>83</sup> However, access to healthcare is suboptimal for many women at highest risk of HIV infection whether residing in high- or low-income countries.<sup>84,85</sup> Hence, possible warning signals of HIV infection such as recurrent vulvovaginal candidiasis or severe PID may not be heeded.

Guidelines for the treatment of HIV, including pregnant and lactating women, have been published.<sup>86–89</sup> Prolonged survival after HIV diagnosis is associated with treatment and follow-up by a healthcare provider with expertise in HIV.<sup>90,91</sup> Some of the

adverse effects associated with highly active antiretroviral therapy (HAART) are different in women than in men. Compared with men, women experience more frequent liver toxicity, especially with nevirapine when the CD4 T cell count is greater than 250 cells/ $\mu$ L,<sup>92</sup> dyslipidemia and fat maldistribution,<sup>93–95</sup> lactic acidosis,<sup>96</sup> and rashes.<sup>97–99</sup> These toxicities may be due to clinically significant gender differences in antiretroviral pharmacokinetics.<sup>100</sup> However, many of the studies examining these differences have been too small to be deemed representative, had only very limited pharmacokinetic data or utilized a retrospective study design. Long-term experience with some of the newer ARV agents is limited. However, certain general statements can be made. For example, efavirenz is the preferred non-nucleoside reverse transcriptase inhibitor in treatment-naïve patients. However, it is also a possible teratogen. Therefore efavirenz should be avoided in a pregnant woman during the first trimester or in a woman who desires to become pregnant or who does not or cannot use effective and consistent contraception.<sup>101</sup> Women taking ARV agents that have drug interactions with oral contraceptives should use an additional or alternative contraceptive method.<sup>87</sup> Gynecological conditions may present threats to health in the HIV-infected woman. HIV-infected women are at increased risk of infection with high-risk HPV serotypes and cervical intraepithelial neoplasia.<sup>60,61,102</sup> This risk is highest among women with CD4 T cell counts less than 200 cells/ $\mu$ L and a plasma viral load of greater than 100,000 copies/mL.<sup>63</sup> It is expected that an increased frequency of cervical dysplasia, greater severity with lower CD4 counts, and higher persistence or recurrence rates after treatment may result in increased risk for progression to invasive cervical cancer in HIV-infected women, if regular screening and treatment are not carried out. In the US it is recommended that HIV-infected women undergo a complete gynecologic evaluation, including assessment of cervical cell cytology for dysplastic or more severe changes, as part of their initial evaluation after HIV diagnosis, with another cytological evaluation 6 months later, and then annually if normal.<sup>80</sup> More frequent screening intervals are recommended for women with mild cytologic abnormalities, after excluding the presence of high-grade dysplasia with colposcopy and negative biopsies, and after treatment for dysplasia. Cytologic screening is generally unavailable to most women in low-resource settings; current and evolving screening strategies in these areas are focusing on alternatives such as visual inspection of the cervix after application of dilute acetic acid or the use of HPV testing.

HPV vaccines have been demonstrated to be safe and effective in HIV-uninfected adolescent females and women; clinical trials focused on clinical efficacy have not been carried out.<sup>103</sup> However, HIV infection is not a contraindication to their use. In many low-resource settings, the cost of the vaccine is currently prohibitive. Although the vaccines have been formulated based upon the most prevalent genotypes present in genital warts and/or cervical cancer in North America, Western Europe, and Australia, the oncogenic genotypes 16 and 18 are associated with about 80% of cervical cancers worldwide.<sup>104</sup>

## HIV in Pregnancy and Mother-to-Child Transmission (MTCT) of HIV

HIV infection during pregnancy is associated with a decline in the absolute CD4 T cell count, almost certainly due to hemodilution, since the CD4 percentage is largely unchanged. There appears to be no increased progression of HIV or increased incidence of HIV-associated opportunistic infections during pregnancy, as compared to HIV-infected non-pregnant women of similar HIV stage. However, HIV infection in women is associated with a 30% decrease in fertility,<sup>105</sup> low birth weight,<sup>106</sup> chorioamnionitis,<sup>107</sup> and a five-fold increase in maternal mortality.<sup>108</sup>

In 2008, an estimated 430,000 children were infected with HIV worldwide.<sup>109</sup> Almost all of these infections were acquired by MTCT. The exact mechanism of MTCT of HIV is unknown. Transmission may occur during intrauterine life, delivery, or breastfeeding. Risk of MTCT appears to be the greatest in the setting of advanced maternal HIV disease.<sup>110</sup> In general, there is a 15–30% risk of MTCT in untreated HIV, with the majority of transmission occurring late in pregnancy at the time of labor and delivery.<sup>111</sup> In low-resource countries where there are no safe and sustainable alternatives to breastfeeding, breastfeeding may account for as much as 40% of all MTCT without ARV prophylaxis. Increased risk of transmission is associated with higher maternal viral load<sup>112</sup>; co-infection with genital conditions that increase the genital tract viral load such as sexually transmitted and associated infections<sup>113,114</sup>; or other infections which increase maternal plasma viral load, such as malaria,<sup>115</sup> preterm birth,<sup>116</sup> prolonged membrane rupture,<sup>117</sup> and smoking<sup>118</sup>; or other substance abuse.<sup>119</sup> In high-resource countries, the risk of MTCT has been reduced to 1–2% or less by the application of targeted antenatal and postnatal prevention strategies.<sup>89</sup> These strategies include recommendations for universal screening for HIV in pregnancy leading to early identification of the HIV-infected pregnant woman,<sup>79</sup> subsequent initiation of ART if a woman needs it for maintenance of her own health or as prophylaxis for prevention of MTCT should she not yet meet indications for treatment,<sup>120,121</sup> elective Cesarean section when viral load is not fully suppressed,<sup>122</sup> and complete avoidance of breast feeding.<sup>123</sup>

The use of replacement feeding is the only way to eliminate MTCT via breast feeding but is only workable in settings where there is clean water, low deaths from diarrheal disease among breast feeding infants, and replacement feeding is affordable, available, and acceptable. Replacement feeding is unrealistic and unsafe in sub-Saharan Africa, for example, where over 90% of the global burden of new pediatric infections exists<sup>123</sup> and infant mortality due to diarrheal diseases is high.<sup>124</sup> In this setting, the focus has been on exclusive breast feeding (i.e., giving only breast milk without additional food or fluids) for the first 6 months of life, when HAART is not available, with weaning only when a nutritionally adequate and safe diet without breast milk can be provided.<sup>125–127</sup>

Data from observational and randomized controlled clinical trials have demonstrated HAART provided as prophylaxis to the breast feeding infant or lactating mother can significantly decrease post-natal HIV acquisition risk.<sup>128,129</sup> Pregnant and lactating women

who require treatment should initiate ART aimed at both decreasing maternal mortality and preventing MTCT of HIV. If the mother does not require treatment, it appears that ART prophylaxis given to the infant and triple-drug prophylaxis for the mother are both safe and effective strategies and are recommended for the duration of breast feeding.<sup>130</sup> Specific regimens for the prevention of MTCT of HIV among breastfed infants have been published,<sup>121,125</sup> and are also covered in detail in Chapter 86, “HIV in Children”.

### Summary

- The feminization of the HIV pandemic is growing with over 50% of cases now occurring in women.
- Over 90% of HIV infections in adolescent girls and women have been transmitted heterosexually.
- Intimate partner violence (IPV) is strongly associated with HIV acquisition.
- Fear of disclosure of HIV sero-status and subsequent IPV may result in delayed diagnosis and treatment.
- Gynecological conditions including PID and uterine cervical dysplasia appear to be worse in HIV-infected women than HIV-uninfected women.
- Side effect profiles for some antiretroviral agents are different in women than in men.
- In 2008, approximately 430,000 children were infected with HIV worldwide most of which occurred by MTCT at the end of pregnancy and during delivery.
- Use of ARV drugs in the mother and infant can decrease MTCT risk from 20–30% to less than 2%.
- Exclusive breastfeeding for the first 6 months of life when extended post-natal ARV infant therapy or safe and clean replacement feeding is unavailable can reduce the risk of MTCT during this period.

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# 86

## HIV in Children

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### Introduction

World Health Organization estimated in 2009 that 2.5 million children younger than 15 years were living with human immunodeficiency virus (HIV); 2.3 million of them in sub-Saharan Africa and that 370,000 new infections and 260,000 HIV-related deaths occurred in those younger than 15 years. Most of these children acquire HIV from their HIV-infected mothers *in utero*, at birth, or via breastfeeding. With successful interventions, the risk of mother-to-child HIV transmission can be reduced to less than 1%.<sup>1</sup> However, such interventions are still not widely accessible or available in most resource-limited countries where the burden of HIV is highest, and an estimated 1000 children become infected with HIV each day. Despite the number of children receiving antiretroviral therapy (ART) in low- and middle-income countries increasing from about 75,000 in 2005 to 275,500 in 2008, and to 360,000 in 2009; this equates to only 38% of the children who require therapy.<sup>2</sup> ART for infants and children living with HIV has changed dramatically from monotherapy in the 1990s to current use of combination regimens, typically highly active antiretroviral therapy (HAART).

ART in children has been shown to be effective in increasing survival, reducing opportunistic infections, and improving growth and neurocognitive functioning in all clinical settings whether resource-rich or -poor.<sup>3</sup>

As of February 2009, a total of 25 antiretroviral drugs have been approved for use in HIV-infected adults and adolescents; 16 of these have an approved pediatric treatment indication and are available as a pediatric formulation or capsule size (See Table 86.1).

### HIV and Breastfeeding

Prevention of mother-to-child transmission (MTCT) of HIV has been highly successful in well-resourced countries. However, MTCT continues to occur in under-resourced settings due to lack of funds for effective prevention programs. Transmission from breast milk remains a major mode of MTCT. The probability

of transmission of HIV through human breast milk is estimated at 0.00064 per liter of milk ingested and 0.00028 per day of breastfeeding.<sup>4</sup> A longer duration of breastfeeding is associated with an increased risk of HIV transmission. The monthly probability of late HIV transmission through breastfeeding after the age of 1 month is estimated to be 6.5–8.5 transmissions

**Table 86.1:** Pediatric Antiretroviral Drugs

Class	Drug name	Pediatric formulation
<b>Non-nucleoside reverse transcriptase inhibitors (NNRTI)</b>	Nevirapine (NVP)	S, ST
	Efavirenz (EFZ) ≥3 yrs	C, T, S
	Etravirine (ETR)	Not yet licensed in children
<b>Nucleoside/nucleotide reverse transcriptase inhibitors (NRTI/NTRTI)</b>	Abacavir (ABC) ≥3 mo	S, ST
	Didanosine (ddI)	P, C
	Emtricitabine (FTC)	S, C
	Lamivudine (3TC)	S, ST
	Stavudine (d4T)	C, P
	Tenofovir (TDF) >12 yrs only	T
	Zidovudine (AZT)	S, ST, C, IV
<b>Integrase inhibitor</b>	Raltegravir (RGV)	Not yet licensed in children
<b>Protease inhibitors (PI)</b>	Atazanavir (ATV) ≥6 yr with RTV boosting	C
	Darunavir (DRV) ≥6 yr with RTV boosting	T
	Fosamprenavir (FOS-APV) ≥2 yr	S, T
	Lopinavir/Ritonavir (LPV/RTV)	S, T
	Nelfinavir (NFV) ≥2 yr	P, T
	Ritonavir (RTV) >1 mo	S, C, T
	Saquinavir (SQV)	Not licensed in children
	Tipranavir (TPV) ≥2 yr with RTV boosting	C, S
<b>Fusion inhibitor</b>	Enfuvirtide (T-20) (≥6 yr)	I
<b>Entry inhibitor</b>	Maraviroc (MVC)	Not yet licensed in children
<b>CCR5 antagonist</b>		

Abbreviations: C, capsule; S, oral solution/suspension; ST, scored tablet; T, Tablet; P, powder for oral solution; I, Injectable; IV, intravenous.

per 1000 exposed infants.<sup>5</sup> A randomized clinical trial from Kenya demonstrated HIV transmission through breastfeeding and prevention of such transmission with formula feeding (36.7% and 20.5%, respectively).<sup>6</sup>

For women with known HIV infection living in well-resourced settings, the best approach to prevent postnatal transmission is to avoid breastfeeding. This approach is not feasible or safe for most HIV-infected women in resource-poor settings because of cost, unsafe water supply, and stigma associated with not breastfeeding. Depriving the infant of essential nutrition and immunologic defenses found in breast milk places the infant in a resource-poor setting at increased risk of mortality with a 2.6–5.8 fold increase in the first 6 months and, 1.4–1.8 fold increased risk of mortality in the second 6 months of life associated with formula feeding.<sup>7</sup> If complete avoidance of breastfeeding is not feasible, exclusive breastfeeding where the baby receives only breast milk for the first 6 months of life significantly reduces MTCT.<sup>8</sup> Additionally, early weaning from breast milk (e.g., at 6 months of age), if feasible, would limit the duration of exposure to HIV-infected breast milk thus preventing more than 85% of transmission due to breastfeeding while allowing the child to experience the early benefits of breastfeeding.<sup>9</sup>

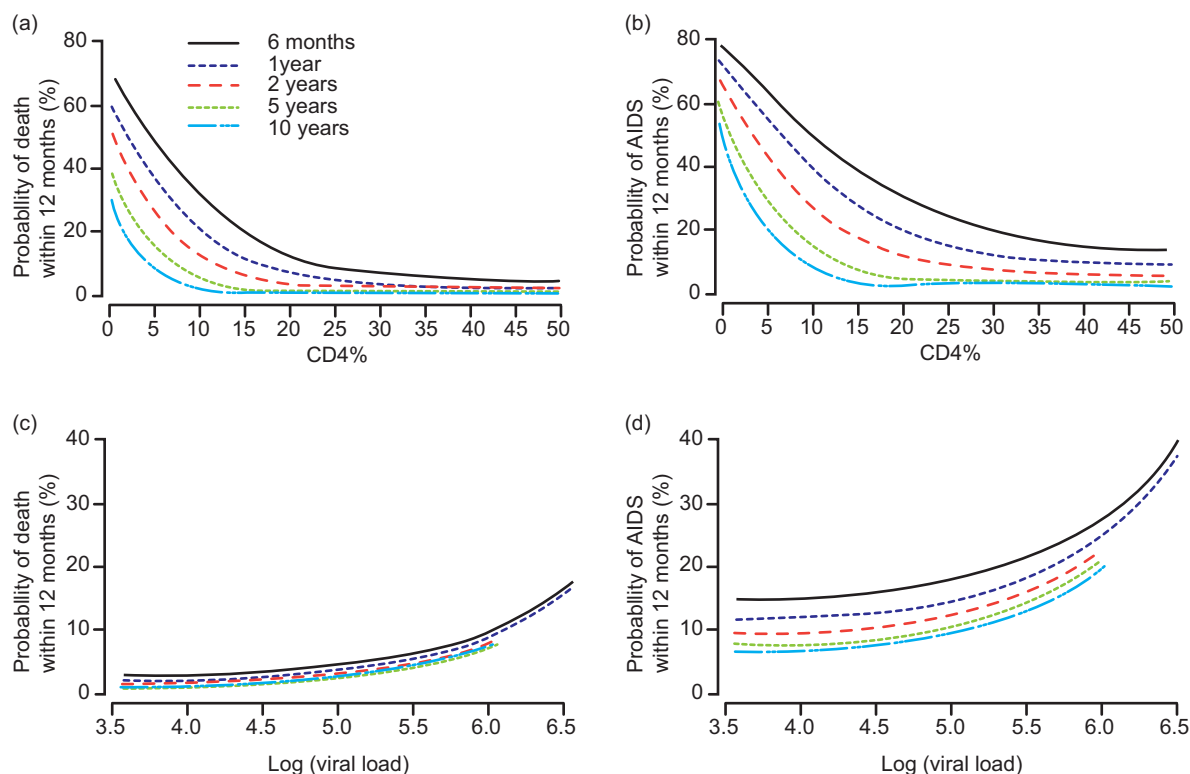
Studies examining intervention strategies to make breastfeeding safer in HIV-infected women have been conducted. Prolonged use of antiretroviral prophylaxis to either the mother or the infant can substantially reduce the rate of MTCT in a breastfed population. In the Kisumu breastfeeding study, ART was given to breastfeeding women from 34 weeks gestation until 6 months postpartum. Infants received single-dose nevirapine (NVP) at birth. The overall rate of transmission in infants was 3.9% at 6 weeks, 5.0% and 5.9% at 6 and 12 months postpartum, respectively.<sup>10</sup> In Malawi, the role of infant prophylaxis during breastfeeding was explored in the NVAZ trial with infants randomized to either single-dose NVP or single-dose NVP plus zidovudine for 1 week with prolonged breastfeeding. At 6–8 weeks, in babies who were HIV negative at birth, 34 (7.7%) babies who had NVP and zidovudine and 51 (12.1%) who received only NVP were subsequently found to be infected ( $p = 0.03$ ). In the PEPI trial where infants were randomly assigned to one of three regimens: single-dose NVP plus one week of zidovudine (control regimen) or the control regimen plus daily extended prophylaxis either with NVP (extended NVP), or with NVP plus zidovudine (extended dual prophylaxis) until the age of 14 weeks with cessation of breastfeeding at 6 months.<sup>11</sup> At 9 months, the estimated rate of HIV-1 infection (the primary end point) was 10.6% in the control group, as compared with 5.2% in the extended-NVP group ( $p < 0.001$ ) and 6.4% in the extended-dual-prophylaxis group ( $p = 0.002$ ). These trials provided evidence that interventions such as maternal and infant antiretroviral prophylaxis, to allow breast feeding during the critical first 6 months of life, followed by early weaning after the intervention is stopped can reduce HIV MTCT. Kafulafula et al. compared mortality outcomes from the various arms of both trials and found that HIV-uninfected infants in the PEPI trial were at significantly increased risk of serious gastroenteritis-related hospitalization and mortality

when compared with HIV-uninfected infants in the NVAZ trial where breastfeeding was prolonged.<sup>12</sup> There is accumulating data from other African nations that the reduction in postnatal HIV transmission that might be expected by early weaning may be countered by increases in serious gastroenteritis-associated morbidity and mortality associated with early cessation of breastfeeding. In Kuhn's Zambian study, one-half of the cohort was randomized to wean abruptly at 4 months while the other was randomized to continue breast-feeding. Weaning during the interval encouraged by the protocol (4–5 months of age) was associated with a 2-fold increased risk of mortality, 6–11 months of age was associated with a 3.5-fold increase, and weaning at 12–18 months of age was associated with a 4.2-fold increase when compared to prolonged breastfeeding.<sup>13</sup> Shortening the normal duration of breast-feeding for uninfected children born to HIV-infected mothers living in low-resource settings is associated with significant increases in mortality extending into the second year of life.<sup>13</sup> Intensive nutritional and counseling interventions reduce but do not eliminate this excess mortality. Heat-treated expressed breast milk is no longer considered a main feeding option in under-resourced settings. The 2010 WHO infant feeding guidance document states that heat-treating expressed breast milk of HIV infected mothers may be considered an interim feeding strategy in some circumstances.<sup>14</sup>

## Natural History of HIV in Children

The impact of effective ART in HIV-infected children is well established. Infants in particular have a higher short-term risk of disease progression and mortality than older children and adults. In the pre-ART era, 20% of infants in industrialized countries developed AIDS and 10% died within the first year of life. The remainder had a 4.7% per annum progression to AIDS or death. At 6 years, 75% of infected children were still alive with around half being alive at 10 years of age.<sup>15</sup> With the introduction of ART, a reduction in mortality in children by 70–80% has been shown in many cohorts.<sup>16</sup> Typical early signs of HIV include lymphadenopathy, candidiasis, chronic parotitis, hepatomegaly, splenomegaly, failure to thrive and developmental delay. Common opportunistic infections (OIs) include *Pneumocystis jiroveci* pneumonia, fungal infections, bacterial infections (especially with encapsulated organisms), mycobacterial infections and recurrent herpes zoster. In infants who acquire HIV perinatally, the mean plasma HIV RNA level in the first year of life is 185,000 copies/mL, significantly higher than in adults, while rapid progression and death is predicted by plasma HIV RNA greater than 299,000 copies/mL. Regardless of plasma HIV RNA level, a CD4 cell count of less than 15% is highly predictive of disease progression and death.<sup>16,17</sup> For children up to 12 years of age, a risk calculator estimating the 12-month risks of progression to AIDS and death, based on the patient's age and one of the following markers: CD4 percent, CD4 count, total lymphocyte count, or viral load can be found on the HPPMCS (The HIV Paediatric Prognostic Markers Collaborative Study) website.<sup>18</sup>





**Fig. 86.1:** Meta-analysis of data from 3941 European and American children (HPPMCS) prior to highly active antiretroviral therapy. The estimated probabilities of death within 12 months by selected age and CD4 percentage (a) and viral load (c) and the estimated probabilities of AIDS by selected age and CD4 percentage (b) and viral load (d) are shown. (Reproduced with permission from Elsevier, Dunn D. *Lancet* 2003;362:1605–11).<sup>19</sup>

Use of combination therapy after 1996/97 has resulted in significant reduction in mortality and morbidity in both adults and children. De Martino et al. evaluated the effectiveness of combination therapy on survival among 1142 children with HIV from 106 Italian centers and showed over 30% reduction in risk of death in the period 1996–98 when dual therapy became widespread.<sup>16</sup> A meta-analysis of survival data from 3941 European and American children, pre-ART, gives risks of disease progression or death at different ages according to presenting CD4 count or viral load, the former being the stronger predictor (Fig. 86.1).<sup>19</sup> CHER data reported a 75% reduction in mortality in those infants who started ART before symptoms or CD4 decline, with a rapid decrease in CD4 values, rapid disease progression, and sudden death all evident among infants in the deferred-therapy group.<sup>20</sup> A decrease in mortality rate by 80–93% in the post-ART era has been observed in the UK, hospitalization rates decreased by 80%.<sup>21</sup>

## Management of Infected Children: General Pediatric Considerations

Special considerations in management of HIV-infected children include:

- Diagnosis
- Age-specific differences in CD4 T cell counts
- Changes in pharmacokinetic parameters with age

- Differences in clinical and virological manifestations
- Immunization issues
- Adherence issues
- Availability of pediatric formulations

Healthy young children have higher CD4+ cell counts than adults which slowly decline to adult levels by about the age of six years, thus age-appropriate CD4+ counts should be used.

Decisions regarding management of HIV in infants and young children have often been based on percent rather than absolute CD4 counts because CD4 % is not age dependent. A recent study by Dunn et al., however, suggested that CD4 % had little or no prognostic value over and above absolute CD4 cell count, irrespective of age.<sup>22</sup>

Infants in particular differ from adults in body composition, renal excretion and liver metabolism causing substantial differences in drug distribution and clearance. Antiretroviral dosing is dependent on weight and body surface area and maintaining ART dosing accuracy in line with rapid growth in early childhood can be challenging, with high levels of under dosing reported.<sup>23</sup>

Standard childhood vaccination schedules should be followed with the exception of BCG which should not routinely be given to HIV-infected children due to the risk of disseminated BCG infection. MMR vaccine is routinely administered to HIV-infected children at 12 months unless they have severely impaired immunity. Influenza vaccine is recommended even in symptomatic HIV-infected children.

## Diagnosis of HIV Infection in Infants and Children

### CHILDREN <18 MONTHS

HIV-DNA PCR is currently the diagnostic method of choice for perinatally exposed children under 18 months of age. Umbilical cord specimens should not be used as contamination by maternal blood can occur. Sensitivity is less than 40% at less than 48 hours of age, and increases to greater than 90% by 2–4 weeks of age.<sup>24</sup> A positive DNA PCR must be confirmed by a second virological test obtained from a separate sample taken more than four weeks after birth.

For infants followed up from birth, US guidelines recommend testing within 48 hours of birth, at 14–21 days of age, 1–2 months, and again at 4–6 months. WHO has recommended HIV-1 DNA or RNA testing within the first 14 days of life, at 1–2 months of age, and again at 3–6 months of age.

Breast fed infants cannot be shown to be HIV uninfected until at least one month after weaning.

### CHILDREN >18 MONTHS

HIV diagnosis requires positive HIV-1 antibody detection tests—positive ELISA and confirmatory test (Western blot or immunofluorescence) (Table 86.2).

## When to Initiate Therapy in Antiretroviral-Naïve Children

Some useful guidelines for the use of antiretroviral agents in pediatric HIV infections are available (see Box 86.1). The current recommendations for initiation of treatment designate four age groups—infants, children aged 1 to younger than 3 years, children aged 3–5 years, and children aged >5 years (Table 86.3).

### Box 86.1 Useful Guidelines of HIV Management in Children

**US guidelines** can be accessed via <http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?guidelineID=8&ClassID=1>

**International readers** should refer to WHO; <http://www.who.int/hiv/pub/paediatric/infants2010/en/index.html>

**Paediatric European Network for Treatment (PENTA)**  
[http://www.pentatrials.org/HIV\\_759.pdf](http://www.pentatrials.org/HIV_759.pdf)

**Table 86.2:** WHO Case Definition for HIV Infection\*

#### Adults and children 18 months or older

HIV infection is diagnosed based on:

- Positive HIV antibody testing (rapid or laboratory-based enzyme immunoassay) and confirmed by a second HIV antibody test (rapid or laboratory-based enzyme immunoassay) relying on different antigens or of different operating characteristics

and/or;

- Positive virological test for HIV or its components (HIV-RNA or HIV-DNA or ultrasensitive HIV p24 antigen) confirmed by a second virological test obtained from a separate determination

#### Children younger than 18 months:

HIV infection is diagnosed based on:

- Positive virological test for HIV or its components (HIV-RNA or HIV-DNA or ultrasensitive HIV p24 antigen) confirmed by a second virological test obtained from a separate determination taken more than four weeks after birth
- Positive HIV antibody testing is not recommended for definitive or confirmatory diagnosis of HIV infection in children until 18 months of age

\*Referenced from 2006, WHO Case Definitions of HIV Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related disease in adults and children. Available at: <http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf>.

### CHILDREN <12 MONTHS

Risk of disease progression is inversely correlated with age in younger HIV-infected children.

The CHER trial randomized infants born to known HIV positive mothers either to start ART at diagnosis (within 12 weeks) or after development of symptoms, or fall in CD4 count. CHER demonstrated a 75% reduced mortality in infants who started ART before symptoms or CD4 decline.<sup>20</sup> More recently, the WHO has recommended that this be extended to all children diagnosed before their second birthday, although European and US guidelines remain as yet unchanged.<sup>25</sup>

### SYMPTOMATIC CHILDREN AGED >1 YEAR

Antiretroviral therapy should be started in all children aged 12 months or older with CDC clinical stage B or C disease or WHO stage 3 or 4 (Tables 86.4 and 86.5) regardless of CD4

**Table 86.3:** Comparison of Current PENTA, WHO, and US Treatment Thresholds—Criteria for Initiating ART

Age	Staging system	PENTA 2009	US 2011	WHO 2010
0–11 months*		Treat all	Treat all	<24 months: Treat all
12–35 months	Clinical	CDC Stage B or C/WHO Stage 3 or 4	CDC Stage B or C	24–59 months: Clinical—WHO Stage 3 or 4 Immunological—CD4 % ≤ 25% or CD4 count ≤ 750 cells/mm <sup>3</sup>
	Immunological	CD4 % < 25% or CD4 count < 1000 cells/mm <sup>3</sup>	CD4 % < 25%	
35–59 months	Clinical	CDC Stage B or C/WHO Stage 3 or 4	CDC Stage B or C	≥5 yr: Clinical—WHO Stage 3 or 4 Immunological—CD4 count ≤ 350 cells/mm <sup>3</sup>
	Immunological	CD4 % < 20% or count < 500 cells/mm <sup>3</sup>	CD4 % < 25%	
≥5 yr	Clinical	CDC Stage B or C WHO Stage 3 or 4	CDC Stage B or C	
	Immunological	CD4 count < 350 cells/mm <sup>3</sup>	CD4 count < 500 cells/mm <sup>3</sup>	

Consider treating all children when HIV viral load greater than 100,000 copies/mL, regardless of clinical or immunological status.

\*Initiation of antiretroviral therapy is recommended for infants younger than 12 months, regardless of clinical status, CD4 percentage, or viral load.

**Table 86.4:** CDC 1994 Revised Classification System for HIV Infection in Children\*

<b>Category N: Not Symptomatic</b>
Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A
<b>Category A: Mildly Symptomatic</b>
Children with <b>two</b> or more of the following conditions but none of the conditions listed in categories B and C:
<ul style="list-style-type: none"> <li>• Lymphadenopathy (<math>\geq 0.5</math> cm at more than two sites; bilateral = one site)</li> <li>• Hepatomegaly</li> <li>• Splenomegaly</li> <li>• Dermatitis</li> <li>• Parotitis</li> <li>• Recurrent or persistent upper respiratory infection, sinusitis, or otitis media</li> </ul>
<b>Category B: Moderately Symptomatic</b>
Children who have symptomatic conditions, other than those listed for category A or category C, that are attributed to HIV infection. Examples of conditions in clinical category B include, but are not limited to, the following:
<ul style="list-style-type: none"> <li>• Anemia (<math>&lt;8</math> g/dL), neutropenia (<math>&lt;1000</math> cells/mm<sup>3</sup>), or thrombocytopenia (<math>&lt;100,000</math> cells/mm<sup>3</sup>) persisting for <math>\geq 30</math> days</li> <li>• Bacterial meningitis, pneumonia, or sepsis (single episode)</li> <li>• Candidiasis, oropharyngeal (i.e., thrush) persisting for older than 2 months in children aged older than 6 months</li> <li>• Cardiomyopathy</li> <li>• Cytomegalovirus infection with onset before age 1 month</li> <li>• Diarrhea, recurrent or chronic</li> <li>• Hepatitis</li> <li>• Herpes simplex virus (HSV) stomatitis, recurrent (i.e., more than two episodes within 1 year)</li> <li>• HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month</li> <li>• Herpes zoster (i.e., shingles) involving at least two distinct episodes or more than one dermatome</li> <li>• Leiomyosarcoma</li> <li>• Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex</li> <li>• Nephropathy</li> <li>• Nocardiosis</li> <li>• Fever lasting for greater than 1 month</li> <li>• Toxoplasmosis with onset before age 1 month</li> <li>• Varicella, disseminated (i.e., complicated chickenpox)</li> </ul>
<b>Category C: Severely Symptomatic</b>
<ul style="list-style-type: none"> <li>• Serious bacterial infections, multiple or recurrent (i.e., any combination of at least two culture-confirmed infections within a 2-year period), of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)</li> <li>• Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs)</li> <li>• Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)</li> <li>• Cryptococcosis, extrapulmonary</li> <li>• Cryptosporidiosis or isosporiasis with diarrhea persisting for greater than 1 month</li> <li>• Cytomegalovirus disease with onset of symptoms at age greater than 1 month (at a site other than liver, spleen, or lymph nodes)</li> <li>• Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children younger than 2 years of age); c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance</li> <li>• Herpes simplex virus infection causing a mucocutaneous ulcer that persists for greater than 1 month; or bronchitis, pneumonitis, or esophagitis for any duration affecting a child older than 1 month of age</li> <li>• Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)</li> <li>• Kaposi sarcoma</li> <li>• Lymphoma, primary, in brain</li> <li>• Lymphoma, small, noncleaved cell (Burkitt), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype</li> <li>• <i>Mycobacterium tuberculosis</i> infection, disseminated or extrapulmonary</li> <li>• <i>Mycobacterium</i>, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)</li> <li>• <i>Mycobacterium avium</i> complex or <i>Mycobacterium kansasii</i>, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)</li> <li>• <i>Pneumocystis jiroveci</i> pneumonia</li> <li>• Progressive multifocal leukoencephalopathy</li> <li>• Salmonella (nontyphoid) septicemia, recurrent</li> <li>• Toxoplasmosis of the brain with onset at older than 1 month of age</li> <li>• Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: <ul style="list-style-type: none"> <li>a) persistent weight loss greater than 10% of baseline; OR</li> <li>b) downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child <math>\geq 1</math> year of age; OR</li> <li>c) less than fifth percentile on weight-for-height chart on two consecutive measurements, <math>\geq 30</math> days apart PLUS 1) chronic diarrhea (i.e., <math>\geq 2</math> loose stools per day for greater than 30 days), OR 2) documented fever (for <math>\geq 30</math> days, intermittent or constant)</li> </ul> </li> </ul>

\*Referenced from Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43 (No. RR-12):1–20.



**Table 86.5:** 2010 WHO Clinical Staging of HIV/AIDS for Children with Established HIV Infection\*

<b>Clinical Stage 1</b>
<ul style="list-style-type: none"> <li>Asymptomatic</li> <li>Persistent generalized lymphadenopathy</li> </ul>
<b>Clinical Stage 2</b>
<ul style="list-style-type: none"> <li>Unexplained persistent hepatosplenomegaly</li> <li>Papular pruritic eruptions</li> <li>Extensive wart virus infection</li> <li>Extensive molluscum contagiosum</li> <li>Recurrent oral ulcerations</li> <li>Unexplained persistent parotid enlargement</li> <li>Lineal gingival erythema</li> <li>Herpes Zoster</li> <li>Recurrent or chronic upper respiratory tract infections (otitis media, otorrhea, sinusitis, tonsillitis)</li> <li>Fungal nail infection</li> </ul>
<b>Clinical Stage 3</b>
<ul style="list-style-type: none"> <li>Moderate unexplained malnutrition not adequately responding to standard therapy</li> <li>Unexplained persistent diarrhea (14 days or more)</li> <li>Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month)</li> <li>Persistent oral candida (outside first 6–8 weeks of life)</li> <li>Oral hairy leukoplakia</li> <li>Acute necrotizing ulcerative gingivitis/periodontitis</li> <li>Lymph node TB</li> <li>Pulmonary tuberculosis</li> <li>Severe recurrent bacterial pneumonia</li> <li>Symptomatic lymphoid interstitial pneumonitis (LIP)</li> <li>Chronic HIV-associated lung disease including bronchioectasis</li> <li>Unexplained anemia (&lt;8 g/dl), neutropenia (&lt;500/mm<sup>3</sup>) or chronic thrombocytopenia (&lt;50,000/mm<sup>3</sup>)</li> </ul>
<b>Clinical Stage 4</b>
<ul style="list-style-type: none"> <li>Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy</li> <li>Pneumocystis pneumonia</li> <li>Recurrent severe presumed bacterial infections (e.g., empyema, pyomyositis, bone or joint infection, meningitis but excluding pneumonia)</li> <li>Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)</li> <li>Extrapulmonary tuberculosis</li> <li>Kaposi Sarcoma</li> <li>Esophageal candidiasis (or candida of trachea, bronchi or lungs)</li> <li>Central nervous system toxoplasmosis (outside the neonatal period)</li> <li>HIV encephalopathy</li> <li>Cytomegalovirus (CMV) infection, retinitis or CMV infection affecting another organ, with onset at age over 1 month</li> <li>Extrapulmonary cryptococcosis including meningitis</li> <li>Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis, penicilliosis)</li> <li>Chronic cryptosporidiosis (with diarrhea)</li> <li>Chronic isosporiasis</li> <li>Disseminated non-tuberculous mycobacteria infection</li> <li>Acquired HIV associated rectal fistula</li> <li>Cerebral or B cell non-Hodgkin lymphoma</li> <li>Progressive multifocal leukoencephalopathy</li> <li>HIV associated cardiomyopathy or nephropathy</li> </ul>

\*Referenced from WHO Antiretroviral therapy for HIV infection in infants and children: towards universal access. 2010 revision. Annex C. p93. Available at: [http://www.searo.who.int/LinkFiles/HIV-AIDS\\_ARTpaediatricguidelines\\_web.pdf](http://www.searo.who.int/LinkFiles/HIV-AIDS_ARTpaediatricguidelines_web.pdf).

percentage/count or plasma HIV RNA level as they have a higher mortality risk.<sup>26</sup>

### ASYMPTOMATIC OR MILDLY SYMPTOMATIC CHILDREN >1 YEAR

In children aged older than 12 months with clinical stage A or N disease, ART should be started when the CD4 count or percentage falls below age-specific thresholds. In addition, ART should be considered if the viral load exceeds 100,000 copies/mL.

See Table 86.3 for comparison of WHO, CDC, and PENTA guidelines on when to commence ART in children.

### What Initial Combination Therapy for Antiretroviral-Naïve Children

As for adults, first-line ART is usually with 3 drugs from 2 classes—2 nucleoside reverse transcriptase inhibitors (NRTIs) plus either a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI). See Boxes 86.2, 86.3 and 86.4 for summaries of the recommendations.

### WHICH NRTI BACKBONE?

In the US, a combination of abacavir, didanosine, or zidovudine plus either lamivudine or emtricitabine is the preferred NRTI backbone.<sup>27</sup> Lamivudine and abacavir can be given once daily to children older than 3 years, has superior long-term efficacy to lamivudine and zidovudine,<sup>28</sup> and can be given as a fixed dose combination (Kivexa) in older children.

#### Box 86.2 Types of Initial ART Regimens

**NNRTI-based**  
(1 NNRTI + 2 NRTI backbone)

**PI-based**  
(1 or 2 PIs + 2 NRTI backbone)

**3 NRTIs\***  
(ZDV + 3TC + ABC for use only in special circumstance)

\*The preferred first-line ARV regimen for infants and children younger than 2 years of age, who have been exposed to NVP and are taking a rifampicin-containing regimen for TB.

Abbreviations: NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; ZDV, zidovudine; 3TC, lamivudine; ABC, abacavir.

#### Box 86.3 NNRTI-Based Regimens

**Preferred**  
NVP + 2 NRTIs: children aged younger than 3 years or requiring liquid formulation  
EFV + 2 NRTIs: children aged ≥3 years

**Alternative**  
NVP + 2 NRTIs (aged ≥3 years)

**Box 86.4** PI-Based Regimens**Preferred**

LPV/RTV + 2 NRTIs (all ages)

**Alternative**ATV + low-dose RTV + 2 NRTIs (children aged  $\geq 6$  years)FPV + low-dose RTV + 2 NRTIs (children aged  $\geq 6$  years)**Use in special circumstances**

ATV (unboosted) + 2 NRTIs (treatment-naïve adolescents age  $\geq 13$  years and  $>39$  kg who are unable to take RTV [must be boosted with RTV if used with TDF]), FPV (unboosted) + 2 NRTIs (children aged  $\geq 2$  years)

Abbreviations: LPV, lopinavir; RTV, ritonavir; ATV, atazanavir; FOS-APV, fosamprenavir; TDF, tenofovir disoproxil fumarate.

The choice of whether to add a PI or NNRTI to the dual NRTI backbone was addressed in the PENPACT1 Study. No immunological, virological or clinical difference was seen between the treatment groups, with 71% remaining suppressed on first-line therapy at 4 years of follow-up.<sup>29</sup>

With NNRTIs, single-point mutations in the reverse transcriptase gene can cause resistance which may develop after only a few missed doses. Cross-resistance occurs between efavirenz (EFV) and NVP, rendering both drugs futile for future regimens. Etravirine (ETR) a new twice daily NNRTI, licensed in treatment experienced adults is entering phase II trials in children.<sup>30</sup> The correct EFV dose has not been determined in children younger than 3 years and NVP should be used in this age-group. EFV syrup is available, but because of reduced bioavailability, care must be taken as the liquid dose is larger than the capsule dose. Efavirenz can cause neuropsychological side effects and mood swings and is best given at night-time. It is contraindicated in pregnancy and care needs to be taken when prescribing to post-pubertal girls.

PI-based regimens spare NNRTIs and efficacy and potency are well documented. Unlike NNRTIs, resistance requires multiple mutations thus PI-based regimens are less fragile and may be preferable in situations such as adolescence where adherence may be poor.

PI use in children should be ritonavir boosted to optimize drug levels. In children, there is most data on ritonavir boosted lopinavir (LPV/r) (Kaletra) which is also the only PI with both lopinavir and ritonavir combined in either a tablet or liquid formulation.<sup>31</sup> The syrup lacks palatability (contains alcohol 45%). ATV/r (ritonavir boosted atazanavir), fosamprenavir (FOS-APV)/r, tipranavir (TPV)/r, and darunavir (DRV)/r have comparable efficacy with LPV/r in adults. ATV/r and FOS-APV/r are licensed for older children while DRV/r and TPV/r are now licensed for treatment experienced children over 6 and 2 years of age, respectively.

Lopinavir/r (LPV/r) remains the drug of choice for infants and young children ( $<6$  years).

For teenagers ATV/r or DRV/r may be preferable due to once daily dosing. Metabolic complications and multiple drug interactions are potential limiting factors with PI-based regimens. PIs generally have a higher pill burden than NNRTIs.

**TRIPLE-NRTI REGIMEN (ZIDOVUDINE/LAMIVUDINE/ABACAVIR)**

Triple-NRTI regimens should only be considered in special circumstances as they are less potent than NNRTI- or PI-based regimens with higher rates of virological failure. However, they may be considered in children aged less than 3 years with TB co-infection due to interactions of NVP and PIs with rifampicin.

**Prophylaxis Against Opportunistic Infections (OIs)**

Prophylaxis against *Pneumocystis* with cotrimoxazole should be given to all HIV-infected infants from age 1 month until their first birthday.<sup>32</sup> Children aged 1–4 years should receive prophylaxis if their CD4 count is below 500 cells/ $\mu$ L or 20% of total lymphocyte count while children aged 5 years and upwards should receive prophylaxis if they have a CD4 count below 200–250 cells/ $\mu$ L or less than 15%.

**Monitoring of Children on Antiretroviral Therapy**

The aim of ART is to achieve an undetectable viral load ( $<50$  copies/mL plasma) and CD4 reconstitution. Monitoring needs to be more frequent shortly after initiating or changing therapy, but once children are established on treatment and stable, clinic visits can be 3 to 4 monthly.

Therapeutic drug monitoring (TDM) is not widely available for NRTIs as intracellular levels of the active metabolite are complex to measure. TDM of NNRTIs and PIs are useful if there is suspected drug toxicity, poor adherence, drug interactions, or failure to suppress viremia despite apparent good adherence.

**ADHERENCE**

Adherence is of paramount importance for long-term efficacy of ART and infants and younger children rely on caregivers to deliver this. Adherence is particularly poor in adolescence. PI regimens are more suitable in those where adherence is not ideal as PI resistance requires multiple mutations unlike NNRTIs where a single mutation can result in cross class resistance. Once daily medication regimens, choice of formulation and pill boxes/calendars/diaries/peer support can help with adherence.

Drug adherence may be affected more by common side effects, for example, diarrhea due to lopinavir/r, dysphoria caused by efavirenz, nausea due to zidovudine.

**DRUG TOXICITIES**

The common drug toxicities experienced with ART are summarized in Box. 86.5. Longer term side effects of antiretroviral are becoming increasingly apparent as the cohort of children with perinatally acquired HIV infection ages, with many entering adolescence and young adult life exposed to ART for over a decade.<sup>33</sup> Some adverse effects, such as lipid derangements and

**Box 86.5** Common Drug Toxicities

- Hematological adverse events associated with drug-induced bone marrow suppression, e.g., zidovudine
- Mitochondrial dysfunction, primarily seen with NRTI drugs—lactic acidosis, hepatic toxicity, pancreatitis, and peripheral neuropathy
- Lipodystrophy and metabolic abnormalities, primarily seen with stavudine and PIs, and to a lesser degree with NRTIs (fat maldistribution and body habitus changes; hyperlipidemia; hyperglycemia, insulin resistance, diabetes mellitus; osteopenia, osteoporosis)
- Allergic reactions such as skin rashes and hypersensitivity reactions, common with NNRTI drugs, also seen with NRTI drugs, e.g., abacavir

hepatitis, may be due to either ART or HIV itself. Abacavir (ABC) hypersensitivity is associated with the HLA-B5701 allele, and may be fatal if the drug is re-introduced after a reaction. Children with HLA-B5701 should not be given ABC and screening should be adopted as routine practice where possible, particularly in non-Africans.<sup>34</sup>

PIs and the NRTI stavudine have been implicated in the development of fat redistribution syndrome (FRS) and the risk of lipodystrophy and probability of intra-abdominal fat accumulation increase with the duration of PI therapy. NRTIs are associated with lipoatrophy and again development increases with duration of therapy.

Regarding bone health, HIV infection in children has been associated with poor growth, delayed puberty, reduced bone mineral density, and vitamin D deficiency—all factors that may impact on long-term bone health. Concerns about the potential effects of tenofovir on bone mineralization and renal function in children and adolescents exist.<sup>35,36</sup>

Adults with HIV infection are at increased risk of cardiovascular disease (abacavir and to a lesser extent didanosine have been associated with an increased risk of myocardial infarction) and while data is less clear in pediatric populations, comparable risk factors of dyslipidemia, altered glucose metabolism, inflammation and immune activation are increasingly described.

**TREATMENT INTERRUPTIONS**

Potential benefits of planned treatment interruptions (PTI) in children with good CD4 counts include reduced cumulative drug toxicity, possibly reduced viral resistance associated with poor adherence, and improved quality of life.

Largely because of the SMART trial results, treatment interruptions are no longer recommended in adults on suppressive HAART.<sup>37</sup> However, results from the PENTA 11 trial of 109 HIV-infected children, randomized to PTI versus continuous therapy over 72 weeks showed no serious clinical outcomes. On reintroduction of ART younger children had better CD4 % recovery after PTIs and long-term follow-up is ongoing.<sup>38</sup>

**TREATMENT FAILURES**

Treatment failure is defined as suboptimal response or a lack of sustained response to therapy using virologic, immunologic, and clinical criteria.

**Virological failure** is defined as a persistent viral load above 5000 RNA copies/mL, after at least 24 weeks on ART.

**Immunologic failure** is defined as developing or returning to the following age-related immunological thresholds after at least 24 weeks on ART.

- CD4 count of less than 200 cells/mm<sup>3</sup> or % CD4+ less than 10 for a child 2 years or older to younger than 5 years of age
- CD4 count of less than 100 cells/mm<sup>3</sup> for a child 5 years of age or older.

**Clinical failure** is defined as the appearance or reappearance of WHO clinical stage 3 or stage 4 events after at least 24 weeks on ART.

It is important to recognize that not all instances of treatment failure require an immediate change in antiretroviral therapy. Causes need to be addressed, and should include poor adherence to therapy, medication intolerance, inadequate dosing, poor absorption of medications, drug–drug interactions and drug resistance.

In considering second-line therapy, if a child has received initial therapy with an NNRTI-based regimen, change to a PI-based regimen is recommended and vice versa.

New ART regimens following treatment failure should be chosen based on treatment history and drug-resistance testing.

Management of drug resistance can be challenging in treatment-experienced children. Referral to a pediatric HIV specialist is preferred at this stage. Darunavir/rtv, Tipranavir/rtv, and Enfuvirtide(T-20), a fusion inhibitor may be considered where multidrug resistance has occurred and are licensed for children in this setting. T-20 must be administered subcutaneously twice daily and is associated with a high incidence of local injection site reactions (98%).

Where patients are failing on ART regimens approved for their age, use of investigational agents or agents approved for older age groups can be considered. While pediatric data is limited, the combination of etravirine, darunavir/r and the integrase inhibitor raltegravir given to 12 heavily pretreated French adolescents at standard adult doses resulted in 11 patients achieving a viral load of less than 400 copies/mL after a year.<sup>39</sup> Phase II safety and pharmacokinetic studies of raltegravir in treatment experienced children age 2–18 years are ongoing and initial data is encouraging.<sup>40</sup> Etravirine is an NNRTI that may retain antiviral activity even in the presence of NNRTI resistance-associated mutations induced by NVP or EFV. Maraviroc, a CCR5 receptor antagonist acts by blocking R5-trophic HIV entry into CD4 cells and pharmacokinetic, safety and efficacy studies of maraviroc and an optimized backbone in treatment experienced CCR5 tropic 2–17 year olds are ongoing and include a liquid formulation.

Resistance testing should take place while the child is on therapy with a detectable plasma viral load, because predominant



plasma viral strains may quickly revert to wild-type once drug pressure is removed. Thus, if a child with prior therapy develops resistant virus and then stops therapy, wild type virus may dominate in the absence of therapy. In this situation, resuming the prior therapy would fail to suppress the virus because the resistant virus would again emerge.

## Co-Infections in the Setting of HIV—HBV, HCV, TB

### HEPATITIS B (HBV)

There is well-documented interaction between HIV and HBV infection, with increased rates of hepatotoxicity. Some ARVs have activity against HBV (3TC, FTC, tenofovir). ART regimens in co-infected patients should, where possible, contain either two drugs active against HBV (usually TDF with either 3TC or FTC) or none. For adolescents more than 12 years of age with hepatitis B, the preferred regimen is tenofovir (TDF) + emtricitabine (FTC) or 3TC + NNRTI.<sup>41</sup> If HBV requires treatment in a patient whose HIV does not yet require treatment, then use of drugs also active against HIV (e.g., entecavir) without additional ART should be avoided to prevent development of HIV resistance.

### HEPATITIS C (HCV)

HCV co-infection also increases the risk of liver toxicity, but long-term follow-up data for co-infected children is sparse. No anti-HIV ART drugs are effective against HCV; however there is an increased risk of hepatotoxicity with ART which needs to be monitored. In addition, ART can interact significantly with drugs used to treat hepatitis C, e.g., ribavirin.

### TB

There are particular difficulties of TB diagnosis, drug interactions, and immune reconstitution disease in HIV-infected children. The standard treatment with four antituberculous drugs is recommended, but rifampicin significantly interacts with NVP and PIs, generally reducing their drug levels. Rifabutin may be used instead of rifampicin to reduce interactions or EFV-based regimens or triple nucleoside regimens may be used. The relative timing of ART and antituberculous treatment depends on the degree of pre-ART immune suppression. With a CD4 count above 200 cells/mm<sup>3</sup>, it may be possible to treat the TB first and start ART later. However, if the child has significant immune suppression and is at risk of disease progression, ART should not be delayed and a combination of rifabutin with NVP or efavirenz and two NRTIs is advised. Useful information on drug interactions can be found at [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org). The syndrome of immune reconstitution (IRIS) occurs in children with TB, usually developing around 3 to 4 weeks after starting treatment with worsening of respiratory symptoms, particularly in children who have a low pre-ART CD4 count and high viral load and starting ART within 2 months of starting with

TB treatment. ART should be continued, but steroids may be necessary to manage IRIS.

## Management of Pediatric HIV in Resource-Limited Settings

Management in resource-limited settings faces several challenges.

### IDENTIFICATION OF HIV INFECTED CHILDREN NEEDING TREATMENT

The ideal entry point should be at an antenatal clinic with the offer of HIV screening to all pregnant women, and the use of interventions to prevent MTCT of HIV, for example, antiretroviral drugs, caesarean section, and consideration of provision of infant formula in those women found to be infected with HIV. Infants born to HIV-positive mothers should be followed for clinical symptoms and signs of HIV infection and be tested for HIV. In this scenario, infants are identified early and receive ART in a timely fashion. However, in resource-limited settings with a high prevalence of HIV infection, and a large proportion of the pregnant women not knowing their HIV status, physicians should consider screening strategies among infants accessing medical services. In a recent South African study, HIV testing was performed universally in all 6-week-old infants attending the immunization clinic; 9.2% were diagnosed with HIV.<sup>42</sup> In a Zambian setting, routine HIV testing for all hospitalized pediatric patients (median age of 12 months [interquartile range: 0–24 months]) at a university teaching hospital, identified 29.2% as HIV infected.<sup>43</sup>

### ACCESS TO TREATMENT AND CARE

Timely access to treatment poses a great challenge in resource-poor settings for HIV-infected children. Even though current guidelines recommend initiation of ART when CD4 count is less than 350 cells/mm<sup>3</sup> in older children, and CD4 % is less than 25% in younger children, data from meta-analysis of 15 pediatric cohorts in Asia and Africa showed that median CD4 at initiation of ART is only 8.1%.<sup>44</sup>

### ANTIRETROVIRAL DRUGS FORMULA

Large scale implementation of pediatric antiretroviral treatment programs in resource-limited settings has been feasible due to several factors:

- Generic antiretroviral therapy has significantly increased access to treatment
- Efforts to provide pediatric antiretroviral tablets is crucial, despite antiretroviral syrup formulation being more accurate in term of dosing for infants and young children. Owing to high cost, short shelf-life, and difficulties in logistics, syrup formulations are not feasible under many field conditions.
- Currently, there are several solid formulation and pediatric fixed-dose combination (FDC) available for children of vary-

ing size (e.g., Baby FDCs of d4T 6 mg/3TC 30 mg/NVP 50 mg; Junior FDCs of d4T 12 mg/3TC 60 mg/NVP 100 mg). Some are scored or chewable tablets.

- The weight-banded simplified ARV table provided by the WHO working group is very helpful for large scale programmes compared to individual dose calculations using dose per kilogram or body surface area.<sup>45</sup>

## HIGH RISK OF DEVELOPMENT OF IRIS

The risk of IRIS developing is particularly high in children who have a low pre-ART CD4 count and high viral load. The incidence of IRIS among HIV-infected children in resource-limited settings is reported in the range of 19–38%.<sup>46</sup> The common organisms associated with IRIS in children are mycobacteria (tuberculosis, BCG-associated IRIS and non-tuberculosis mycobacterium) and herpes virus infection, for example, cytomegalovirus. IRIS should be considered when patients present with symptoms shortly after commencing ART. Unmasking of IRIS generally requires treatment of the opportunistic infection. Most cases of paradoxical IRIS (i.e., symptoms of IRIS despite appropriate OI therapy) resolve spontaneously, or can be managed with non-steroidal anti-inflammatory drugs. Occasionally IRIS becomes progressively worse and may require a short course of treatment with corticosteroids and rarely, a temporary discontinuation of ART.

## Guideline for First-Line and Second-Line Antiretroviral Therapy for Children in Resource-Limited Settings

WHO 2010 guidelines recommend initiating ART to all children diagnosed before 2 years of age where CD4 testing is not available due to high morbidity and mortality, children 2–5 years with CD4% less than 25% or 750 cell/mm<sup>3</sup> and children older than 5 years with CD4 count less than 350 cell/mm<sup>3</sup>. The recommended first-line regimen is non-nucleoside reverse transcriptase (NNRTI) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs). Monitoring after initiation of ART relies mostly on clinical and immunological indices as access to HIV viral load testing to confirm treatment failure is limited. This leads to late detection of treatment failure and more risk of development of HIV viral mutations associated with multidrug resistance. A report from HIV-infected children with treatment failure detected by HIV RNA monitoring every 6 months showed only 8% with multi-NRTI drug resistance.<sup>47</sup> However when the treatment failure was detected by clinical or immunological criteria, multi NRTI drug resistance was reported to be up to 36%.<sup>48</sup>

The criteria for switching to second-line regimens recommended in the WHO 2010 guidelines are more conservative, using a public health approach, than US or PENTA guidelines, but are based on limited evidence. The immunologic criteria for switching are CD4 count less than 200 cell/mm<sup>3</sup>, or CD4 % less than 10% for

children younger than 5 years, and CD4 count less than 100 cell/mm<sup>3</sup> for children older than 5 years. Virologic failure is defined as HIV RNA greater than 5000 copies/mL. The recommended second-line regimen is re-cycling 2 NRTI plus protease inhibitors. More data are needed on the efficacy of second-line regimens, using WHO criteria, when a high rate of multi-drug resistance NRTI is expected, which may make an NRTI backbone less effective.

## Conclusion

Understanding the principles of selecting ART regimens and vigilance of potential toxicities are essential for optimal management of HIV-infected infants and children. The greatest challenge lies in maintaining adherence to medications so physicians need to advise a regimen which is tolerable, simple yet effective, and potent yet without a huge pill burden.

### Summary

- With successful interventions the risk of mother-to-child HIV transmission can be reduced to less than 1%.
- Breast-feeding should be avoided to prevent postnatal MTCT. However, if not possible, as in some settings, strategies to minimize breast milk transmission include exclusive breast feeding and/or antiretroviral prophylactic regimens (maternal or infant or both).
- ART has markedly reduced mortality and morbidity including improved growth and neurocognitive function among children and adolescents infected with HIV-1.
- CD4+ve lymphocyte %ages rather than absolute count is a more reliable marker of immune status in young children until about six years of age when counts resemble those of adults.
- All infants younger than 12 months of age should start ART regardless of their CD4 % or count, HIV viral load and clinical state.
- In areas where CD4+ve lymphocyte testing is not reliably available, WHO 2010 recommend that children between the ages of 12–24 months also start ART.
- In older children, ART should be initiated based on immunological and clinical parameters (Table 86.3).
- An NRTI-backbone with either a boosted PI or an NNRTI is the preferred regimen in ART-naïve patients.
- PI regimens are more suitable in those where adherence is not ideal as PI resistance requires multiple mutations.
- Dosing in children varies considerably from adults owing to differing pharmacokinetics but ART is generally well tolerated.
- Referral to a pediatric HIV specialist is advised when resistance develops in treatment-experienced children.
- With co-existing TB, the relative timing of ART and antituberculous treatment depends on the degree of pre-ART immune suppression.
- Risk of IRIS developing is high in children with a low pre-ART CD4 count and high viral load.
- Challenges remain in resource-poor countries: identification of HIV in pregnant women, identification of HIV-infected children in need of treatment, access to ART, dual infections particularly TB and high risk of development of IRIS.

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## HIV Infection in Homosexual Men

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### Introduction

On June 5, 1981, the Centers for Disease Control (CDC) (Atlanta, USA) published a report of five cases of *Pneumocystis carinii* pneumonia (PCP) among previously healthy young men in Los Angeles.<sup>1</sup> This report is sometimes referred to as the “beginning” of HIV/AIDS, but it might be more accurate to describe it as the beginning of the general awareness about AIDS in the USA. A few months later, a 49-year-old man was admitted to the Brompton Hospital in London suffering from PCP, thought to be the first case of AIDS in the United Kingdom.<sup>2</sup> The first case of AIDS in Australia was diagnosed in November 1982.<sup>3</sup> Within 18 months, epidemiologists from CDC conducted studies and prepared *MMWR* reports that identified all of the major risk factors for AIDS, and a compendium is available.<sup>4</sup> There then followed dramatic social, public health and clinical responses, graphically described by Randy Shilts.<sup>5</sup>

The epidemiology of HIV is covered elsewhere in this volume in comprehensive detail. For the purposes of this chapter, we have introduced the chronology of HIV in men who have sex with men (MSM)/homosexual men, because all of the present authors began their careers as HIV clinicians at about this time, between the years 1984 and 1987, and have since practiced for many years in one or more of these countries; United Kingdom, United States of America, and Australia. The majority of our patients have been homosexual men, or MSM, although we have treated others, and in other countries.

### Background

Despite figures suggesting that <10% of the male population engaged in same sex activity,<sup>6</sup> MSM are over-represented in the epidemiology of HIV throughout the world.<sup>7</sup> In many developed countries, MSM account for the largest proportion of new diagnoses and in regions such as Asia, for example, the reported proportion of MSM infected with HIV ranges from 10% to 42%.<sup>7</sup>

In the United Nations General Assembly High-Level Meeting on AIDS, in June 2008, fewer countries reported on services for

MSM than for any other. Furthermore, those reports that were made available reflected, lower coverage levels for MSM than for the general population or for other most-at-risk populations (UNAIDS).

Homosexual activities are illegal in most countries and remain heavily stigmatised, even in areas where legal protections exist.<sup>8</sup> Thus, it is difficult to derive truly meaningful figures for the proportions of MSM who are infected with HIV. Convenience samples from locations such as STI clinics typically yield rates of 1–20%<sup>9</sup> and community rates are likely to be lower.

Thus, the majority of MSM are not infected with HIV, yet are often stigmatised as such by the general (and sometimes medical) communities. Even when not infected, awareness of HIV is typically much higher among MSM than in the general community—with correspondingly greater condom usage than in the heterosexual community.<sup>10</sup>

In MSM, HIV infection is most commonly acquired through unprotected anal intercourse (UAI), especially when multiple partners are involved.<sup>11</sup> Thus, it is generally found in the minority of MSM who have UAI in their sexual repertoire, together with frequent partner change. Taking a detailed sexual history is therefore essential in assessing potential risk for HIV infection and for comprehensive care of those already infected.

MSM may not see themselves as “gay”, and heterosexually-identifying men sometimes engage in same sex activities in environments such as prisons.<sup>12</sup> The rapid spread of HIV, hepatitis and other STIs may therefore occur in these conditions as a result of a combination of factors, including: non consensual sexual activity, lack of condoms, illicit drug use, poor access to clean injecting equipment, high background rates of infections in deprived populations, and often inadequate management of those with existing HIV infection.

### Provision of Health Services

Social and political barriers greatly impede the recognition of the extent of the problem of HIV infection in MSM. This, in turn, makes the delivery of effective healthcare difficult and creates

barriers to prevention efforts aimed at reducing the spread of HIV within the MSM community and inevitably, to the wider community. In order to facilitate presentation to MSM-friendly services, there needs to be outreach via good community links, advertising, use of the internet communication and word of mouth. Whether the clinic forms part of a general medical facility or part of a general sexual health service or even a specific MSM-targeted practice, the physical context of the facilities is important. Ideally the clinic should be located with ready access to transport, in an area convenient to the population it serves. The entrance needs to be situated to provide discretion and privacy, yet sufficiently recognizable to the target population, for example by using the internationally recognized “rainbow flag”.

The most important features for the provision of services include:

- i) a confidential and safe environment
- ii) staff that understand the needs of their patients (staff drawn from the MSM community, or others who are sensitive to MSM issues)
- iii) training and expertise in the needs of HIV-infected MSM
- iv) adequate time to address issues

The waiting room and facilities would be ideally decorated in a way to make patients feel comfortable and at ease. This can be achieved by avoidance of harsh lighting, the colors, and friendly communications with the staff.

The waiting room offers an opportunity to provide educational materials such as posters, pamphlets and booklets which can be placed to allow waiting patients reading material and information. It also provides an opportunity to reassure the patients that the staff understands issues such as confidentiality and local aspects of MSM lifestyles. Beyond the clinic, it is important to consider how the internet may be used to enhance services. This may be in a variety of ways, such as sources of reliable information, social networking sites, risk assessments, booking of appointments and results made available.

A detailed knowledge of current and potential risk activities is essential to the appropriate provision of preventative messages, safer sex devices and clean injecting equipment. One of the key skills for the treating physician is therefore, the ability to create an environment of trust, where the patient is clear about confidentiality. However, the potential implications of disclosure of illegal activities need to be explicitly negotiated with the patient. This may impact on areas such as:

- i) disclosure of illegal activity such as “homosexual behavior”, injecting drug use, sex work and under age sexual activity
- ii) notification of HIV positive diagnoses to authorities in identifiable, coded or de-identified formats
- iii) dealing with situations where there may be risks of onwards transmission, including unsafe sexual and injecting behaviors
- iv) lack of disclosure of the HIV status by the patient in sexual, work and social settings

It is thus important to become familiar with the rules of the local jurisdiction.

## Recreational Drug Use

Rates of recreational drug use such as cigarette smoking, alcohol, and illicit drugs are higher in MSM compared to the general population.<sup>13–15</sup> This has a number of potential impacts on HIV infected MSMs:

- i) These lifestyle factors are often associated with other risky behaviours, such as frequent partner change and failure to use condoms.<sup>16</sup>
- ii) Increased risks of cardiovascular disease and malignancies related to smoking are compounded by HIV infection.
- iii) Illicit drug use, particularly drugs such as crack, cocaine, crystal, and methamphetamine, may increase rates of unsafe sexual activity.<sup>17</sup>
- iv) Unsafe injecting may increase the risk of HIV transmission and the acquisition of viral hepatitis. Individuals co-infected with hepatitis may have more rapidly progressing disease. Superinfection with another strain of HIV may cause additional problems, particularly in the context of the acquisition of resistant virus.
- v) The generally chaotic lifestyle usually associated with stimulant drugs such as cocaine and amphetamine, usually leads to major problems with adherence to antiretroviral therapy (ART) and other therapies.
- vi) Certain recreational drugs may impact on the metabolism of prescribed medications, with potentially adverse consequences.
- vii) Sildenafil and similar drugs may be used, either for *bona fide* erectile dysfunction, or to enhance existing sexual performance. Drug interactions may occur with prescribed medications, together with the potential for increased onward transmission of HIV and other STIs.

An accurate history of recreational drug use, including smoking, alcohol and illicit drug consumption is therefore essential to effective management. It facilitates the provision of targeted, appropriate advice to reduce potential harm to the individual and others. However, insistence on abstinence is not only unlikely to result in behavior change, it may have a negative impact on any trust in the therapeutic relationship and reduce the likelihood of any further disclosure of risk activities. The key focus should therefore be on harm minimisation, rather than stopping all activities that are potentially harmful. However, in certain circumstances total abstinence may be the only viable option.

In general, unless the need for antiretroviral drug (ARV) therapy is particularly urgent, dependency issues should be addressed prior to initiation of ART. Patient motivation is crucial for this process to occur. Depending on the extent of the problem, simple advice, specialist counsellors and specific medications may be required. In extreme cases, directly observed therapy has been effectively used to ensure good adherence to



ARVs in patients taking illicit drugs. This is difficult to do, but for patients on methadone programs it is somewhat easier to organize.

## Sexual Practices

A good understanding of sexual practices of MSM is important to be able to effectively provide advice, testing, and management.

Men negotiate sexual partners in a number of different contexts, and, increasingly, via the internet. They engage in a wide variety of sexual practices, many of which are low risk from the perspective of the transmission of HIV and other STIs. In addition to frottage, oro-genital, oro-anal and penile-anal intercourse, MSM may also practise techniques such as sado-masochism, water sports, fisting, the intra-anal insertion of drugs, and scatting. Knowledge of what these practices are, and the potential health and transmission consequences of them, is therefore required to provide informed advice.

“Barebacking” is the term used for unprotected anal sex and is practised by some men who feel that the use of condoms significantly reduces the pleasure of sex. It has significant potential for the transmission of HIV and other STIs. Sometimes it is practised by those wishing to become infected by HIV (to fit in with friends or to remove subsequent concern about being infected), and men doing this are sometimes referred to as “Bug chasers”.

In the 1990s, when it was realized that many new infections were contracted within the context of new relationships, a strategy of “negotiated safety” was developed. This approach involves partners initially testing for HIV and STIs, engaging in only protected sexual activity for a window period (typically of three months), re-testing and, if both negative, considering dispensing with protected activity within the context of the relationship. The level and form of contact activity outside the primary relationship is then negotiated between the partners. This strategy has been successful at reducing HIV infection within the context of new relationships. However, it does require a high level of open and honest communication between partners and may be more suitable for MSM who are gay-identified. In general, though if a sexual indiscretion occurs in a “committed relationship”, the last person to be informed will be the partner. Advice to always use safe sex within a committed relationship should probably therefore always be proffered.

“Sero-sorting” involves seeking partners of the same HIV status. Part of the impetus for this arose as a result of discrimination against HIV positive MSM by HIV negative MSM and their desire to avoid potential rejection when disclosing their status. In this manner, HIV positive men will only have unprotected sex with other men who know they are also infected, but it can still potentially lead to the transmission of other STIs and HIV superinfection. Likewise seroconcordant HIV negative partners can still transmit other STIs and potentially acquire HIV if a participant is unaware of their HIV status or seroconverting. Seronegative consensual unsafe sex actually is dangerous for HIV transmission as well. If a man becomes acutely infected

with HIV it is at that time that his viral load is the highest and that transmission is most likely to occur (several papers having postulated that the majority of transmission in fact occurs from acute seroconverters). A man unknowingly undergoing seroconversion may fairly recently have had a negative HIV test and will tell prospective partners that he is “HIV negative”.

“Strategic positioning” may be chosen in the context of known HIV sero-discordant partners. The HIV positive partner adopts the receptive position during anal sexual activity, reducing the risk of HIV transmission. This may reduce risk somewhat but of course most heterosexual men contract the disease from active sex so it is at best only partly protective for the active partner. Many physicians, and several guidelines, now recommend treating the positive partner of a serodiscordant MSM couple, as treatment for prevention—regardless of what the man’s immune status (CD4 count) may be.

Sero-sorting thus relies on partners knowing their HIV status and being honest in the disclosure of their status, where this is known. The window period involved in HIV testing and the greater transmissibility of HIV during the time of primary HIV infection reduce the reliability of sero-sorting as a strategy. Despite these potential drawbacks, sero-sorting has had some success in reducing HIV transmission, but is less effective than use of condoms, and does not prevent the transmission of other STIs.

Although large randomized trials in Africa have conclusively demonstrated a potentially useful role for male circumcision in the prevention of HIV and other STI transmission in the heterosexual community,<sup>18–22</sup> the evidence for value in MSM is less clear.<sup>23</sup> This is not surprising since it would theoretically only benefit those men whose sexual repertoire only included an insertive role.<sup>23–26</sup>

## Emotional Needs

Once a person becomes HIV-positive, previously fit young men may experience profound loss of control over their life and this may compound issues of low self esteem. Approval may be lost from loved ones, including family. They also have to suddenly deal with the medicalization of life, with a whole new world of knowledge, rules, tests and medications.

HIV positive MSM may be quite socially isolated and lack good social support. They may also be reluctant to disclose their status to others in the MSM community, because of justifiable fears of ostracism. Furthermore, disclosing one’s HIV status may impact on the ability to find partners and there may be legal obligations to do this prior to engaging in any form of sexual activity. The development of facial lipodystrophy may effectively disclose HIV status and some men may avoid starting ART because of fear of it. With the avoidance of the use of thymidine-analog NRTIs in ART, the patient can be reassured that the occurrence of lipodystrophy is very unlikely. If lipodystrophy has occurred, men may understandably, seek out cosmetic procedures to improve their appearance. Concealment of medications may

also be necessary to avoid their discovery, and this may compound difficulties with adherence.

Finding a doctor who listens, works with the patient and has the requisite medical expertise, may be difficult, but is critical to effectively face the many challenges of HIV infection. Appropriate support, counselling, and social services may have profound benefits.<sup>27</sup>

## Developing Countries

Because of stigma against MSM activity, the contribution of MSM-acquired HIV infection is often under-reported in developing countries and may not be accurately reflected in national surveillance data. Only ten countries worldwide (in North America, Europe, Australasia, and Africa) currently have legislation recognizing same sex relationships on an equal footing as heterosexual ones. Even in these parts of the world, discrimination may still cause significant problems in delivering effective healthcare and prevention strategies. According to The International Lesbian and Gay Association,<sup>28</sup> 78 countries actively criminalize consensual same sex acts among adults (2009 data), and most other countries adopt some form of discriminatory legislation. This is despite the fact that in some areas, such as Latin America, MSM contact is the predominant method of HIV transmission. In countries of Eastern Europe, Asia and Africa, rates of HIV in MSM are significantly higher than in the general population.

MSM, more frequently than in the developed countries, may not identify as “gay,” depending on local social mores, and different degrees of openness. As a consequence, MSM sexual activity is frequently clandestine, with even marriage to a woman and parenting. Such behaviors may therefore facilitate spread of HIV to the heterosexual community.

MSM may be at particular risk of HIV in developing countries for a number of reasons, including:

- i) poor knowledge regarding safer sex practices,
- ii) psychological denial of their risky practices,
- iii) lack of access to condoms and lubricants,
- iv) high background rates of other STIs,
- v) reluctance to seek healthcare for fear of discrimination,
- vi) low testing rates, with consequent lack of knowledge of HIV status, and
- vii) commercial sex work.

Healthcare workers in developing countries therefore have many challenges delivering effective HIV care to MSM as a result of stigma, legal difficulties and reluctant colleagues. More research is clearly required to identify optimum methods of delivery.

## Asia

Unprotected sex in MSM with multiple partners is one of the three main modes of transmission of HIV in the Asia-Pacific region, the other two being unprotected sex in the context of sex work, and unsafe injecting drug use.<sup>29</sup> There are several million MSM in the Asian region.<sup>30</sup>

MSM are up to 25 times more likely to be living with HIV compared to the general population.<sup>31</sup> MSM in urban areas of Thailand, Cambodia, and Myanmar are experiencing severe HIV epidemics with prevalence >10%. MSM in cities in Vietnam, Laos, Indonesia, China, Nepal, and India face intermediate level epidemics with prevalence of 2–10%.<sup>30</sup> Emerging epidemics in MSM are now evident in Pakistan, Bangladesh, East Timor, and the Philippines. There are also alarming rates for other STIs, particularly syphilis (for example 11% among MSM in China: Chen XS, personal communication). A series of amFAR documents in 2007–2009<sup>32,33</sup> pose the question, when so many resources are devoted to HIV, how could the entire international community have overlooked or simply ignored the rapidly rising rates of HIV infection among MSM? Part of the answer it seems lies in the stigma and violence surrounding MSM; in Asia and the Pacific, eleven countries have laws that criminalize consensual sexual activity among persons of the same sex. Institutionalization of a “culture of hatred” results in covert and overt discrimination and a denial that sex between men actually occurs. “The generalized discomfort with male-to-male sex has helped generate a familiar vicious cycle; no data equals no problem; no problem equals no intervention; and no intervention equals no need to collect data”.<sup>34</sup> For much of the last decade less than half the countries in the region did not include MSM in any form of sentinel data collection, nor include MSM in their national AIDS plans.

It is clear that there are diverse MSM identities in Asia; a glossary that would include transgender, overtly feminine acting MSM, overtly masculine acting MSM, gay men, men who have situational sex with other men. In other words there is a continuum; and it may be very difficult for outsiders, perhaps especially, western epidemiologists, to grasp the nuanced nature of MSM in Asian countries. In terms of sexual behaviours, a kaleidoscope of multiple unions is possible. Multiple sex partners are a common theme, however, and condoms may have to take second place to fleeting encounters, or indeed, emotional desire.<sup>35</sup>

A number of key researchers have been sounding the alarm on MSM and HIV in Asia for some time.<sup>31,36,37</sup> Many non-governmental organizations (NGOs) have also been active, for example Family Health International, which has supported several initiatives,<sup>38</sup> which resulted in an important and innovative resource—Practical Clinical Guidelines for Sexual Health Care of Men who have Sex with Men; these are available on the IUSTI Asia Pacific website.<sup>39</sup> The challenges for MSM programs are various and include the fact that many MSM do not identify as such and so are hidden from MSM-specific programming, as well as continuing prejudices.

Recently, there have been some crucial surveys and documents that support major funding for MSM in Asia, with specific attention to these issues.<sup>30,32,33</sup>

## Pacific

In the Pacific region, on the other hand, gender inequality and gender-based violence are considered to be the major drivers in the spread of HIV and STIs largely in the heterosexual community.

Nevertheless, male-to-male sex, also a key risk, is often hidden and denied.<sup>40</sup>

Therefore, one of the key recommendations<sup>35</sup> is engaging MSM, and those individuals of other “culturally-constructed”, genders in more high quality and participatory research that can be translated into effective prevention programmes.

## Africa

In Africa, the overwhelming scale of the heterosexual epidemic, coupled with the political, social, and cultural barriers against homosexuality, have meant that an MSM-focused response to HIV has been absent across the continent.<sup>41</sup>

It is not surprising that population-level data on MSM in Africa are rare. Same sex relationships are criminalized in 37 out of 54 African countries, and are punishable by death in four of these.<sup>42</sup> In this environment, misconceptions about the potential risks of MSM transmission are easily perpetuated. Another finding across a number of African studies is a high level of bisexual concurrency, with MSM often reporting having both male and female partners.<sup>43</sup>

In summary, scholarly work in recent years has clearly documented that, alongside of the global heterosexual epidemic, most developing countries have significant, if under-recognized, MSM epidemics.<sup>44</sup>

## Prevention of Transmission

Effective prevention of HIV transmission in the context of MSM has several key components:

- i) *Raising the awareness about HIV* acquisition in those at risk, without the use of unnecessarily alarmist language.
- ii) *Education with regards to safer sexual practices.* This includes the use of condoms for anal sex and in the case of oral sex, not taking ejaculate orally. Condom usage within the MSM community in developed countries is relatively high and continues to be one of the most effective methods to prevent HIV transmission. However, even within this community condom usage is becoming less common, with up to 40% of MSM having engaged in unprotected anal intercourse in the past year in certain US cities.<sup>45</sup> Less conscientious safer sex practices may occur in younger MSM (with little direct experience of HIV and AIDS), older MSM (with “safer sex fatigue”), those ending long term relationships and re-engaging in sexual activity, and in those entering new relationships (where the experiences of emotional safety are confused with biological safety). The degree of condom usage within a community is also dependent on the community acceptance of condoms. This can perhaps be influenced by developing prevention programs to develop peer support for condom-protected sexual activity.
- iii) *Reduction in the number of partners.* This is dependent upon cultural norms, but can potentially be influenced by peer education. However, it should be noted that unprotected anal intercourse, even in the context of serial monogamy, may still result in transmission. It should be noted that abstinence

as a method of prevention of HIV transmission has been found to be ineffective in both MSM and heterosexual sexual transmission.<sup>46,47</sup>

- iv) *Avoiding sexual contact* in areas involving open wounds, ulceration and recent dental work.
- v) *Easy access to free, confidential HIV testing*, with those at risk encouraged to undergo this frequently. Potential barriers to this include possible legal ramifications of not disclosing one’s status to potential partners and lack of confidentiality regarding results.
- vi) *Regular testing and prompt treatment of STIs*, particularly Genital Ulcerative Diseases (GUDs) such as HSV, syphilis and lymphogranuloma venereum. GUD increases risk of transmission when this occurs in the HIV co-infected person, and increases the risk of transmission to the HIV negative person via increased viral shedding, and via disruption to the mucosal integrity and/or recruitment of HIV-susceptible inflammatory cells. The rates of GUD are higher in MSM compared to the general population. For example, HSV2 seroprevalence is estimated to be 25–50% in MSM and higher in MSM with HIV positivity (50–70%). Among men who have sex with men (MSM), reported seroprevalences of HSV2 vary as a marker of HIV status: high (80%) prevalences are observed among those co-infected with HIV, while lower (20–50%) seroprevalences are reported for those not infected with HIV.<sup>48,49</sup>
- vii) *Routine testing:* The Centers for Disease Control in the USA currently recommend a policy of routine testing for HIV in STD clinics, emergency departments, hospital wards and physician offices, to try and identify a greater percentage of HIV infected individuals. Such identification would mean more infected people could be reached with safe sex education, and treatment, and would hopefully significantly decrease transmission and the number of new infections. This policy however has not been significantly implemented due to physicians discomfort with offering the test and the lack of reimbursement for routine testing.
- viii) *Early initiation of ART.* From a public health perspective, lowering HIV plasma viral load may lead to a community reduction of transmission, although undetectable plasma viral load does not mean zero risk of HIV transmission. Cases of transmission of HIV when the viral load is <1000 copies/mL have, however, rarely been reported. Population modelling has demonstrated the theoretical feasibility of such an approach.<sup>50,51</sup> There has even been a suggestion<sup>52</sup> that condom usage can be dispensed within discordant couples, where the HIV infected partner has consistent plasma virological suppression on ART. In response to this there is a Swiss consensus statement asserting that people with HIV infection receiving effective antiretroviral treatment (i.e. with undetectable HIV viral load) and without an STI, cannot transmit HIV through sexual contact.<sup>53</sup> A recent consensus statement by the



Australasian Society for HIV Medicine (ASHM), the National Centre for HIV Epidemiology and Clinical Research (NCHECR), Australian Federation of AIDS Organisations (AFAO), and the National Association of People Living with AIDS (NAPWA)<sup>54</sup> strongly cautions against HIV prevention based solely on ART. One of its key recommendations is to encourage further research into HIV transmission, including the role of co-infection with other STIs

- Mathematical modelling demonstrated that risk of HIV transmission in heterosexual partnerships in the presence of effective antiretroviral treatment is low, but not zero. While among male homosexual partnerships the risk transmission is high over repeated exposures.<sup>55</sup>
- However, dispensing with condoms in the presence of HIV plasma viral suppression has not been validated in a MSM population. With increasing evidence of the benefits of earlier treatment of HIV infection in terms of reducing both AIDS related and non AIDS related co-morbidities, there is a developing convergence to treat HIV at diagnosis with the additional benefit of assisting in the reducing HIV. So far this is only theoretical.<sup>56</sup> However, studies are being developed in the United States and elsewhere to formally evaluate this concept by actively treating all of those identified with HIV infection in a community employing routine testing. One such study funded by the National Institutes of Health (NIH) and the US Centers for Disease Control and Prevention will start this year in Bronx, New York, and Washington DC, and will compare outcomes with four matched US cities.<sup>57</sup> The initial study will primarily test the feasibility of such an approach. If successful, it is hoped that future studies will more formally assess the efficacy of widespread and early antiretroviral therapy in eradicating HIV transmission in large populations.<sup>58</sup>

- ix) *Postexposure prophylaxis.* The use of antiretrovirals within 72 hours of potential occupational exposure to HIV is now well-established, and its value is being explored following sexual and injecting encounters. However, the cost, potential toxicities and concerns regarding the encouragement of further risky behaviors has so far limited its deployment. Nonetheless, it does potentially provide an opportunity for risk reduction counselling.
- x) *Pre-exposure prophylaxis.* The use of antiretrovirals (either topically or systemically) before sexual intercourse, or continuously in high risk individuals, for prevention, is currently being researched, but many express concerns that such a program could lead to less condom usage and, if used intermittently, could lead to high levels of ARV resistance to the ARVs used.

NGOs and community organizations frequently have grass roots contacts and experience within affected communities. They are thus able to shape messages that encourage practices which

reduce HIV transmission in language and images which resonate with the specific target group. They may also have a role in the distribution of condoms and water based lubricants at places where MSM meet. The use of NGOs may allow politicians to distance themselves from appearing to support activities which, while evidence-based and effective prevention strategies, are disapproved of by vocal sections of their electorate.

To deliver effective and reliable messages on methods of reducing HIV transmission in MSM populations, the engagement of the community is essential. This allows information to be given in a culturally appropriate, non judgemental manner which addresses the needs of the particular community. The ability to engage with the MSM community and provide these messages is often affected by local moral forces in the form of religious prohibitions, social discrimination and legal restrictions. In some developing countries, those distributing information on safe sex practices and providing condoms and lubricants, have themselves been targeted and subject to criminal sanctions. Measures to decriminalise MSM sexual activity, reduce stigma against MSM, and provide health services and education, can be an important method of combating HIV in the communities and countries affected.<sup>7</sup>

## Management of HIV Infection

The principles of management of HIV infection in the general population also apply to the management of HIV in MSM. For individual patients, the aim is to assess their suitability for ART, mainly on the basis of clinical status, CD4 T lymphocyte count and viral load.

Treatment guidelines worldwide increasingly favour earlier initiation of antiretroviral therapy in HIV-infected individuals.<sup>59–62</sup> The benefits conferred by early treatment are substantial, and include more successful immune reconstitution; lower mortality; lower risk for cardiovascular disease, malignancies, and other complications; improved outcomes of certain HIV-related conditions; slower progression of hepatitis B and C co-infection; attainment of higher CD4 counts on treatment; and lower rates of treatment side effects and HIV drug resistance. The current consensus is to initiate treatment before CD4 levels drop below 350 cells/ $\mu$ L.

ART typically consists of combination therapy involving three drugs, most commonly two nucleosides/nucleotides, with a non nucleoside or a boosted protease inhibitor. Success of therapy is measured by achievement and maintenance of plasma HIV RNA suppression. Consistent adherence is crucial to success, although there are a number of other factors that should also be considered.<sup>63</sup>

## GENERAL MEDICAL MANAGEMENT ISSUES

Evidence accumulated from large cohort studies in developed countries reveal that with combination antiretroviral therapy, mortality and morbidity in HIV infection improves with significant falls in progression to AIDS.<sup>64,65</sup> Mortality from AIDS

and non-AIDS co-morbidities such as cardiovascular, hepatic, renal disease and cancer was higher in the presence of HIV viraemia found during treatment interruptions in the SMART study.<sup>66</sup> Improved survival has led to an increasing age of Western HIV cohorts, and the normal diseases associated with ageing are found at an earlier age in HIV positives. The contributing factors for accelerated ageing include inflammation from low level HIV viremia and immune dysregulation, lifestyle factors such as smoking, alcohol and drugs, co-infections such as hepatitis B and C, and possibly toxic effects of antiretroviral therapy.<sup>67</sup> While prognosis has improved substantially over the years, particularly for those on therapy where CD4 count could be durably increased to normal levels, expected lifespan is expected to be shortened by at least 10 years compared to the average population.<sup>68,69</sup> The implications of ageing for MSM with HIV who are part of a particularly youth-orientated culture are profound and largely unexplored.

Depending on the age of the MSM, a number of general health considerations should be considered, regardless of the HIV status of the man. These include screening for cancers of the prostate, testes and colon, together with cardiovascular assessment. However, it should be noted that access to screening services may be negatively impacted because of some of the issues and challenges related to culturally sensitive care for gay men discussed above.<sup>60</sup> Regular exercise should be encouraged for cardiovascular health, but some men may also require advice regarding the consumption of anabolic steroids and dietary supplements. Excessive weight may be associated with a number of health problems, including diabetes, hypertension, and ischaemic heart disease.

Depression and anxiety appear to affect MSM at higher rates than in the general population,<sup>70</sup> an effect that may be compounded by social isolation and HIV infection. Adolescents and young MSM may be at particularly high risk of suicide because of these concerns. Culturally sensitive mental health services targeted specifically at MSM may be more effective in the prevention, early detection, and treatment of these conditions.

### SPECIFIC ISSUES FOR HIV-INFECTED MSM

Table 87.1 summarizes some of the common challenges faced in the management of HIV positive MSM.

#### Hepatitis A (HAV)

Improving levels of sanitation in many countries in the last two decades have led to a fall in childhood infection, with a concomitant rise in adults susceptible to symptomatic disease and outbreaks. HAV is mainly transmitted through the fecal-oral route. There have been numerous reports of HAV outbreaks among MSM, including in Australia.<sup>71</sup> In Europe, HAV transmission among MSM is endemic. A recent molecular epidemiologic study revealed that 10 HAV outbreaks among MSM in 7 European countries between 1997 and 2005 actually represented one large outbreak among interconnected MSM communities.<sup>72</sup> In the general Australian population the

**Table 87.1:** Common Conditions of HIV-Positive MSM

Condition	Examples
Common conditions of all HIV-infected adults, regardless of method of acquisition	<i>Pneumocystis jiroveci</i> pneumonia and other opportunistic infections, tuberculosis, nephropathies, lymphomas, and treatment-related toxicities
Age-related conditions	Especially in developed countries where widespread use of ARV has resulted in extended life expectancy, for example cerebrovascular disease
Intra-anal and perianal sexually transmitted infections	Condyloma acuminata (anogenital warts) <i>Treponema pallidum</i> (syphilis) <i>Neisseria gonorrhoeae</i> <i>Chlamydia trachomatis</i> Herpes simplex virus types 1 & 2 Lymphogranuloma venereum Tropical ulcers
Sexually transmitted gastrointestinal conditions	Hepatitis A <i>Entamoeba</i> spp. (especially <i>E. histolytica</i> ) <i>Shigella</i> spp. <i>Campylobacter</i> spp. <i>Cryptosporidium</i> spp. <i>Giardia duodenalis</i> <i>Enterobius vermicularis</i> <i>Strongyloides</i> <i>Rectal spirochaetosis</i>
Other common anorectal conditions	Perianal dermatitis Haemorrhoids Abscesses Fissure Fistulae Anal laxity Rectal prolapse
Tumours resulting from STIs	Kaposi's sarcoma, anal cancer
Associated with common risk activities	Hepatitis B & C (from recreational drug use and sexual transmission)
Psychological and psychiatric morbidities	Potentially exacerbated by stigma, ostracism and a direct effect of HIV in the CNS. May be compounded by recreational drug use

Further details of some of these conditions are given below.

seroprevalence is 41%,<sup>73</sup> whereas in a recent cohort of MSM it was 68%,<sup>74</sup> a figure that was thought to represent higher vaccination rates, rather than infection. Adults infected with HAV are more likely to develop icteric hepatitis, although mortality remains generally very low. An interaction with HIV has not been described, even in immunocompromised patients. The rare circumstances in which HAV infection has a significant mortality is when it occurs in older people (>40 years), or those with chronic liver disease, such as that due to HCV, HBV, or alcohol. All MSM should be vaccinated against HAV if antibody negative on screening.

## Hepatitis B (HBV)

HBV is very efficiently transmitted sexually during heterosexual and homosexual contact. Before the HIV/AIDS epidemic, up to 50–70% of homosexual men had serological evidence of past or present infection with HBV.<sup>75</sup>

However, there is evidence that the incidence of HBV infection in gay men has decreased markedly since the early 1980s, associated with the adoption of safe sex, and the advent of an effective HBV vaccine. For example, in Australia, the seroprevalence of core antibody has decreased from 61% in 1982 to 38% in 1991 to 19% in 2004.<sup>74,76,77</sup>

Moreover, in an observational cohort of 2218 HIV-infected MSM (mostly) on antiretroviral therapy in 2003, the seroprevalence was only 4.8%.<sup>78</sup> However, HBV transmission is endemic among HIV-infected MSM in Europe.<sup>79</sup> Vaccination against HBV is highly recommended for all MSM, although it is less effective in HIV-infected individuals.<sup>80</sup> Post-vaccination testing for HBV surface antibody is recommended, and vaccine non-responders should undergo repeat immunization with a full series. The benefit of double dosage, the appropriate strategy for HIV-infected patients with isolated core antibody, and the timing and number of vaccinations in persons with advanced immunosuppression on highly active antiretroviral therapy remain controversial.<sup>81</sup>

The diagnosis of HIV/HBV co-infection is usually made via detection of hepatitis B surface antigen (HBsAg), but since immunodeficient individuals may be negative, it is recommended that they also be tested for the presence of anti-core antibody (anti-HBc). If either is present, patients should be evaluated for active HBV replication, using an assay for HBV DNA.

The importance of HIV/HBV co-infection lies in the profound effects of HIV on the natural history of HBV infection; it is not cleared as efficiently; the prevalence of chronic HBV is 25%, compared to 3–5% in HIV-seronegative MSM with HBV.<sup>82,83</sup> Presumably, this could have an important effect on the epidemiology of HBV.<sup>84</sup> Despite the high levels of HBV replication, co-infected patients have significantly lower serum alanine aminotransferase levels than those with chronic HBV alone, and yet progression to cirrhosis is more common.<sup>82</sup>

In contrast to the effect of HIV on HBV infection, most studies have not detected a significant effect of HBV infection on the clinical course of HIV infection,<sup>84,85</sup> or on the rate of antiretroviral treatment change.<sup>78</sup>

The management of HIV/HBV co-infection is complex, and best left to experts in the field. Sustained suppression of serum HBV DNA to below the level of detection by the most sensitive assay should be the goal of therapy and at present treatment of HBV in this setting is life-long. Close monitoring is necessary to detect failure or hepatic flares, particularly following initiation of combination antiretroviral therapy (cART). It is worth remembering that severe hepatotoxicity occurs in up to 10% of all patients commenced on cART, and that all antiretrovirals

have been associated with abnormal liver function, particularly ritonavir, nevirapine, and tipranavir, whose use should be avoided. Most of the drugs used to treat HBV infection (eg lamivudine, telbivudine, adefovir, tenofovir, entecavir) have some *in vitro* activity against HIV, and both viruses can be treated with a simplified combination of drugs (usually containing tenofovir and emtricitabine). A more detailed discussion on management can be found elsewhere.<sup>86,87</sup>

## Hepatitis C (HCV)

The sexual transmission of HCV has generally been considered to be inefficient as estimated by cross-sectional studies in populations usually considered to have a high prevalence of STIs. In a national survey of 17,000 GUM clinic attendees in London in 1995,<sup>88</sup> only 1% were positive for HCV. In a cohort of 1038 homosexually active men in Sydney between 1984 and 1989,<sup>89</sup> 7% were seropositive for HCV; moreover, being positive was associated with IDU and/or HIV, but not sexual behaviour.

However, in a series of case reports and large clusters, it is apparent that there has been a recent epidemic of HCV among HIV-infected MSM in Europe and Australia.<sup>90–93</sup> The vast majority of cases deny IDU, but most have been associated with high risk sexual behaviours that are more likely to be associated with anal trauma; hence they have been designated “per-mucosal”. 250 strains from Europe and Australia were subjected to a molecular phylogenetic study.<sup>94</sup> A “molecular clock” analysis suggested that the majority of transmissions (85%) occurred since 1996; temporarily then, this epidemic coincides with the introduction of highly active antiretroviral therapy (HAART), and some increases in high risk sexual behaviours. It is speculated that apart from possible impaired immunological control of HCV and/or increased viral load in semen,<sup>95–97</sup> the largest risk factor in these cases is an increase in high risk sexual behaviours, including large numbers of partners, seroconcordant sexual partnering (sero-sorting), disinhibition with recreational drug use etc. These speculations have recently been extensively reviewed.<sup>98</sup>

Most MSM with HCV report a combination of various, potentially high risk, sexual and drug practices. The interaction between sex and drugs is complex, and many of these factors are highly correlated and difficult to disentangle. Intranasal and rectal drug use in itself could favour HCV transmission via shared contaminated implements. It is more likely however, that the association with drug use reflects residual confounding: unmeasured sexual risk behaviour due to disinhibition and sexual arousal. Based on current knowledge, sexual transmission of HCV is probably mediated by factors such as traumatic sexual techniques and ulcerative STIs that may cause mucosal damage in the rectum. However, it is striking that the recent outbreak almost exclusively affects HIV-infected MSM; the HCV incidence in HIV-negative MSM is still low, indicating that these men remain largely unaffected. Therefore, it is also likely that the



immunological changes associated with HIV are contributing to the changing epidemiology. First, HIV perturbations of the GI immune system have become a major focus for the immunopathogenesis in HIV, so it is conceivable that defects in mucosal immunity are also facilitating permucosal transmission of HCV.<sup>99</sup>

In addition, defects in cell-mediated responses are associated with reduced HCV clearance, and higher HCV viral loads in serum and semen.

In Sydney, Australia, the most recent estimates of HIV/HCV co-infection are 9.39% and 12.8%, and come from a cohort of HIV-infected men, and an observational database of HIV-infected persons on treatment.<sup>78,100</sup>

The major impact of HIV/HCV co-infection on the natural history of HCV is the acceleration of liver disease progression.<sup>101</sup> Co-infection is associated with a higher mortality than mono-infection with either virus alone. Prior to the HAART era, the high mortality from AIDS-related causes predominated, and masked any other causes for mortality. However, as effective therapy for HIV became available and AIDS-related mortality declined, liver-associated mortality emerged as the second most frequent cause of death, especially in those with co-infections, often with excessive use of alcohol as a cofactor. Co-infection is associated with lower rates of spontaneous HCV clearance, accelerated liver disease, and less favourable disease outcomes. However, it has recently been shown in an Australian study that treatment outcomes can be improved if started early.<sup>102</sup> The diagnosis of HCV infection is made by the detection of HCV antibody and the detection of HCV RNA by polymerase chain reaction (PCR) in serum. HCV genotyping is important, as some genotypes are relatively resistant to therapy and prolonged treatment is required. Decisions regarding management are complex, and include drug toxicities, patient preference, and adherence. In general, people with significant immunodeficiency should be treated with cART first; others with preserved immune function can receive treatment for HCV first. In HIV-negative individuals, acute HCV is almost always treated with PEG monotherapy; in HIV-positive individuals, there has been greater variation, with a general trend towards the use of combination therapy with ribavirin, although there is little evidence to support this, and it may add significant risk of toxicity and drug interactions. In the future, there is likely to be a paradigm shift using HCV protease and polymerase inhibitors.

## Syphilis

After an initial decline in the 1980s, coincident with the advent of AIDS, syphilis has emerged as a major problem in the 1990s in MSM in Australia,<sup>103,104</sup> United States,<sup>105</sup> Europe,<sup>106,107</sup> China,<sup>108</sup> and other less developed countries.<sup>109</sup> It has disproportionately affected MSM with HIV-infection; in Australia the rate in homosexual men with HIV is 5–10 times higher than in HIV-negative men. The reasons for this

are unclear; early syphilis is transiently associated with low CD4 counts and a high viral load, these return to baseline levels with treatment.<sup>110</sup> Many investigators have suggested that it reflects higher levels of unprotected sexual activity among gay men with HIV-infection.<sup>12,111</sup>

There are higher rates of asymptomatic syphilis, and higher rates of relapse if untreated; moreover individuals with HIV are more likely to present with secondary syphilis than those without HIV.<sup>112</sup> Oral sex is established as an efficient method of transmission.

Notwithstanding the conventional use of serology, with its small but significant numbers of false positives (due to polyclonal B-cell stimulation) and false negatives, (due to the prozone phenomenon, or lack of an immune response), a significant number of laboratories are utilizing PCR techniques for lesional syphilis.<sup>113,114</sup>

Neurological involvement of syphilis in HIV co-infection manifesting as acute syphilitic meningitis, ocular disease and more rapid progression to tertiary syphilis, has been found more frequently than in syphilis mono-infection, particularly with plasma RPR  $\geq 1:32$  or CD4 count  $\leq 350$  cells/ $\mu$ L.<sup>115,116</sup>

Re-infection is possible and is detected by an increasing non-treponemal assay titer.<sup>117</sup> Three-monthly testing is recommended for persons at high risk,<sup>118</sup> and modelling exercises have shown this period to be optimal for gradually reducing the epidemic; these recommendations will likely be extended to all HIV infected men. Contact tracing is very important; any contact within 90 days of early syphilis should be presumptively treated with benzathine penicillin.

Other aspects of the diagnosis and management of syphilis in HIV-infected individuals are covered comprehensively in Chapter 84.

## Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) has been recognised as an endemic cause of genital ulcer disease in Africa and Asia for many years. However, since 2003, it has emerged in Western countries as an infection of significance in MSM, particularly those with HIV infection. It has the potential to enhance HIV and HCV transmission because of its ulcerative and inflammatory nature. In addition to its association with HIV, LGV infection is also associated with the presence of other STIs, anal enema use, unprotective anal intercourse, use of sex toys, and fisting. It is caused by infection with *C. trachomatis* serovars L1, L2, and L3, particularly L2b and diagnosis requires biovar specific testing of *C. trachomatis* positive specimens. Unlike regular chlamydial infection (caused by serovars D-K), LGV is associated with a clinically more aggressive course, symptomatic proctitis, invasive infection with a predilection for regional lymph node involvement, and in some cases tissue inflammation resulting in fistula formation, and systemic symptoms may occur. Involvement of inguinal or femoral nodes may result in suppurative infections called “buboes”. Recommended therapy is 21 days of doxycycline 100 mg bd.<sup>11,119–122</sup>

## Increased Risk for MRSA Skin and Soft Tissue Infections among HIV-Infected Persons

HIV-infected persons have an elevated risk for both MRSA (methicillin-resistant *Staphylococcus aureus*) colonization and infection. Recent studies from USA suggest that patients with HIV have an 18-times higher rate of MRSA infections than the general population.<sup>123</sup> Clinical manifestations mirror those seen in the general population; most patients present with skin and soft tissue infections (SSTIs) including furuncles, abscesses, and/or cellulitis. Complicated disease may also occur, including necrotizing soft-tissue infections, fasciitis, bacteremia, and endocarditis.<sup>124–126</sup>

The reasons for the increased risk for MRSA infections among HIV patients is unknown, but it may be related to an increased use of antibiotics in this population (e.g. beta-lactam antibiotics), intravenous drug use, high-risk sexual behaviours, and poor immune status. In addition to the higher risk for MRSA infections, HIV-infected persons also appear to have a high risk for recurrent SSTIs after an initial MRSA infection; this may be due to persistent colonisation, e.g. nasal or even perineal, carriage.<sup>127</sup> Studies involving novel carriage sites as well as the effectiveness of decolonisation strategies are needed.

The management is conventional, namely incision and drainage, and treatment with an antibiotic that may need to be modified after susceptibility testing. Initial choices include cotrimoxazole, doxycycline, clindamycin or intravenous antibiotics such as vancomycin. Given the high risk of recurrence, patients should be counselled to present early with any new skin lesion that may represent MRSA.

## Circumcision and Male-to-Male Transmission

In 2006, Drain<sup>128</sup> evaluated relationships between male circumcision (MC) prevalence, Muslim and Christian religion, and seven infectious diseases using country-specific data among 118 developing countries. In multivariate analyses among non-sub-Saharan African countries controlling for religion, higher MC prevalence was associated with 8.94-fold decrease in the adult HIV-prevalence among countries with primarily heterosexual HIV-transmission, but not, as expected, among countries with primarily homosexual or injecting drug use HIV-transmission.

However, analyses of available observational and cohort studies of MSM<sup>23,24,26,129–131</sup> revealed insufficient evidence that male circumcision protects against HIV infection, or other STIs.

The absence of clear evidence of a protective effect of circumcision against HIV and other STIs in MSM may be the consequence of the failure of past studies to stratify analyses by subjects' anal sexual role. MSM can practice exclusively insertive anal sex, exclusively receptive anal sex, or not engage in anal intercourse at all. Because receptive anal sex

poses the greatest per-contact risk for HIV acquisition<sup>132</sup> and circumcision would not affect the risk through being exposed to HIV as a receptive partner, it has been hypothesized that the protective effects of a circumcision would vary, based on a man's anal sexual behavior. Men who are primarily the insertive partner during anal intercourse would benefit most from circumcision, men who were versatile during anal intercourse would receive some protection, and those who were primarily the receptive partner would receive little or no protection.

### Summary

- MSM with HIV are over-represented but under-recognized in many countries. However, most MSM do not have HIV.
- MSM activities are illegal in many countries contributing to stigma, failure to seek healthcare and reluctance to disclose risk activities.
- Targeted prevention strategies are most effective that include MSM community involvement and those that reduce stigma and discrimination.
- Higher rates of co-morbidities including STIs, drug and alcohol issues and mental illness are found in MSM with HIV.
- Medical services providing confidential and supportive care attuned to the needs of MSM facilitate disclosure and enhance capacity to control the epidemic.

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# HIV in Blood and Blood Product Recipients

Roger J. Garsia

88

## Current Scale of Medically Acquired HIV Infection

Concerns about the potential for donor derived blood products to transmit chronic viral infection initially centered on hepatitis B virus in the mid 1970s and after introduction of screening for hepatitis B surface antigenemia attention shifted to non-A, non-B hepatitis infection by the end of that decade.<sup>1</sup> HIV contamination of the therapeutic blood and tissue supply in the late 1970s and early 1980s was unrecognized initially,<sup>2</sup> and led to a serious and widespread epidemic of medically acquired HIV infection.<sup>3–6</sup> Identification of antibodies to Lymphadenopathy Associated Virus (LAV, later renamed HIV) in those with AIDS, and in seemingly healthy carriers,<sup>7</sup> was pivotal in provoking action to protect the global blood supply. During the 1980s most reports of screening in blood product exposed hemophiliac cohorts, conducted in developed and medium-income countries showed HIV antibody prevalence of 70% or more in the hemophiliacs who had been the greatest users of coagulation factors.<sup>6,8</sup> At a sub-population level, the severity of coagulation factor deficiency in developed countries generally correlated with rates of cumulative blood product exposure, and consequently HIV transmission risk.

In most cases infection was sub-clinical, without what is now recognized as HIV seroconversion illness symptoms. Consequently, the diagnosis of infection in HIV-exposed individuals was not made reliably until highly specific serology became widely available,<sup>8</sup> and cohorts of blood product recipients were screened for the synonymous HTLV-III/LAV/HIV in lookback programs undertaken as an urgent priority in the mid 1980s.<sup>9</sup> In the intervening period, secondary transmissions to sexual partners were not rare, and the consequences of HIV infection devastated many families and catalyzed international action against discrimination. Measures operating at many levels were taken to protect the blood supply from ongoing contamination. Principally, safety was improved by donor selection, antibody-based screening for HIV, and then post-collection virus inactivation procedures of the blood products. Heat and detergent-based virus inactivation treatment was only

feasible for a limited range of plasma-derived products to reduce the risk of viral transmission,<sup>10</sup> and there were no chemical or physical treatments suitable for decontaminating whole blood, or cell products derived from blood.

## Impact of Donor Screening with High Sensitivity Antibody Tests

In those developed countries which instituted rigorous donor selection followed by serological screening for HIV antibody, new HIV infections in recipients of blood, fractionated blood products, or tissues became rare.<sup>11</sup> Confidence in the safety of blood has resulted in high rates of growth of blood product use in developed countries, for example, the number of hospital admissions involving blood transfusions more than doubled (140% increase) over a 10-year period 1997–2007 in the US<sup>12</sup>; currently in that country, in 2010, it is estimated that over 16 million separate donations will be collected from 9 million plus donors. Although data are often unavailable for low-income countries, the trends in usage are upwards. Coping with the escalating costs of ensuring a safe blood supply has been a challenge for many jurisdictions. Many poor countries were not able to introduce serological testing of individual donors till the 1990s, and, even some 25 years after availability of HIV screening serologically, not all countries have quality-assured screening for 100% of donations<sup>13</sup>; WHO data show many nations are still dependent on paid donors for plasma and blood supplies. Furthermore, many blood banks do not use assays capable of detecting HIV antigenemia and rely only on detecting antibody to HIV, a testing algorithm that leaves the blood supply vulnerable to an approximately three-week window period of pre-seroconversion infectivity from donors with newly acquired HIV.

More than a quarter of a century after the availability of HIV serology, occasional cases of very long standing transfusion-acquired HIV, whose acquisition can be traced back to the era prior to blood donor screening, are still being diagnosed.<sup>14</sup> Despite the many advances in diagnostic HIV testing and the use of NAT technology, which shortens the average screen-

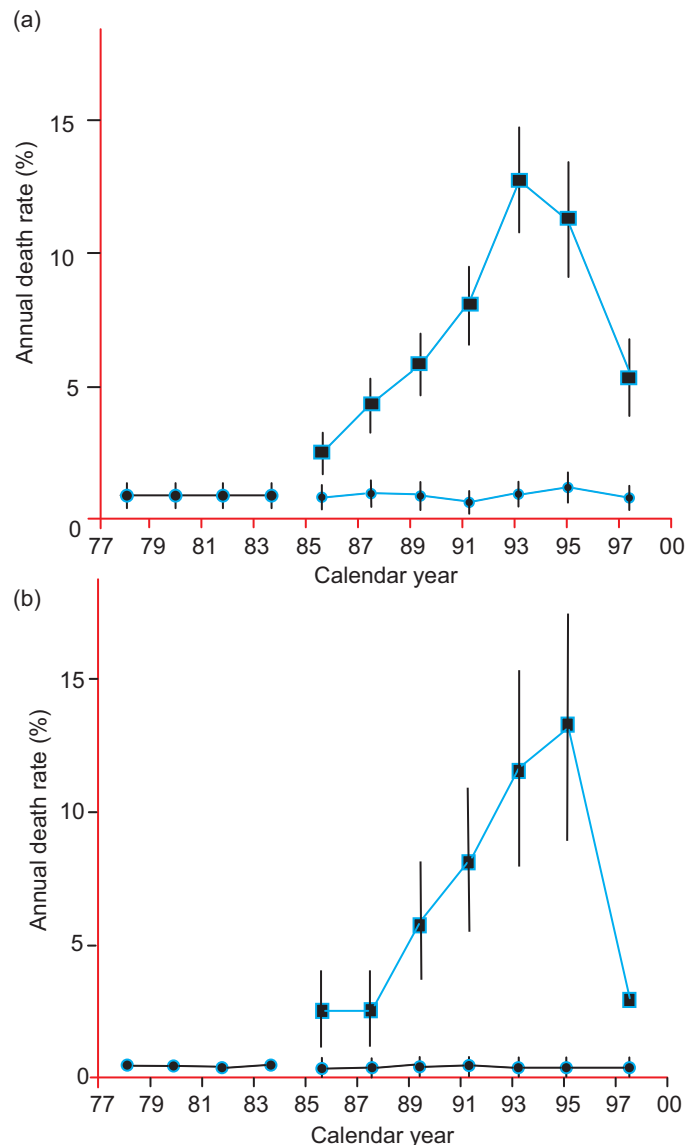


negative window period to about 10 days, HIV transmission still occasionally occurs from blood products of donors whose HIV infection has eluded the most sophisticated of modern screening tests.<sup>15</sup> Awareness of the potential for virus screened blood products to transmit infection remains high among medical practitioners in most countries, particularly those with paid donors and a high HIV-prevalence in heterosexual populations, including intravenous drug users. Unfortunately the general population has a much poorer understanding of the risks inherent in transfusion. Internationally significant efforts are continuing to promote the importance of quality-assured universal testing of all donated units of blood. However vigilance in excluding virus screen-negative, potentially contaminated units, based on behavioral questionnaires of donors, is still an important though controversial element of success in containing the spread of HIV by blood and tissue products.<sup>16</sup>

The vast majority of cases of medically transmitted HIV were diagnosed in the decade immediately following their acquisition, as a result of high rates of uptake of the newly developed first-generation enzyme linked immunosorbent assay for HIV antibodies used as screening tests from the mid 1980s.<sup>17</sup> Many campaigns urging those who were blood product exposed to present for testing were directed at hemophiliacs and other frequent transfusion recipients. From lookback campaigns came important data unequivocally linking the development of HIV infection, and in some cases AIDS, in recipients with carriage of the same virus in donors.<sup>18</sup> One well studied transmission cluster provided evidence that some donor-recipient pairs progressed similarly slowly when infected with naturally attenuated virus deficient in the *nef* region of the HIV genome.<sup>19</sup>

### Altering Natural History of HIV in Medically Acquired HIV with Antiretroviral Therapy

From the time of available HIV serology the medical profession was exhorted to seek out possible recipients of contaminated blood sourced material.<sup>20</sup> Thus many of those diagnosed with HIV after screening were asymptomatic, but sufficiently immunodeficient by CD4 T cell numerical criteria, to warrant antimicrobial prophylaxis of opportunistic infection and early access to antiretroviral therapies in clinical trials or compassionate access programs. As new agents and classes of antivirals emerged from the pharmaceutical industry's drug-development programs, long infected, highly drug experienced patients, such as those with blood product related HIV, were frequently among the first to use them. The success of combination antiretroviral therapies has led to the current situation, whereby the survivors of transfusion and transplantation related HIV are now, in the second decade of the 21<sup>st</sup> century, almost exclusively of adult age, and highly antiviral-treatment experienced; many have been HIV infected for over 25 years (Fig. 88.1).<sup>17</sup> With the demographic features of very long duration HIV, and facing a significantly shortened life expectancy, they present the treating clinician with a complex set of management considerations.



**Fig. 88.1:** The impact of HIV on UK hemophilia cohorts. Age standardized annual male death rate for all UK hemophiliacs whose hemophilia was severe (a) or mild/moderate (b) and whose HIV status was unknown in 1977-1984 (circles) or known in 1985-1999 to be HIV positive (filled rectangles) or HIV negative (filled circles). *Source:* Darby SC, Kan SW, Spooner, et al.<sup>17</sup>

Those who acquired HIV at a very young age, whether from contaminated blood products or from vertical transmission, displayed variable patterns of progression to immunodeficiency and AIDS. A subgroup of these never reached their teenage years.<sup>20</sup> In contrast, those infected during teenage and early adulthood tended to have a better prognosis than older adults, and many more of them have survived, supported by access to effective HAART from the mid 1990s. Many have reached middle age, where they face the impact of ageing coupled with the impact of the biological effects of HIV and its treatment. Long-term survivors now form a large proportion of the category of those currently living with HIV acquired from blood products.<sup>17</sup>

## Co-infection with HIV and Hepatitis Viruses

Data emanating from hepatitis C screening of national and international cohorts of HIV positive hemophilia patients revealed the high rates of hepatitis C virus co-infection,<sup>21</sup> and in some centers triple infection was documented with both hepatitis C and hepatitis B complicating HIV in a small proportion of patients.<sup>22</sup> Thus medical management in transfusional HIV has been frequently complicated, and not infrequently dominated, by the co-morbidity of chronic viral hepatitis.<sup>23</sup> Furthermore, many of the HIV and hepatitis infections in hemophiliacs were acquired from large batch donor-pooled products. Consequently they were at risk for acquiring multiple quasispecies of HIV, and/or multiple genotypes of hepatitis viruses.<sup>24</sup> On the other hand, cell product recipients, other than those with need for repeated transfusion, frequently had single donor -sourced virus infection, and most escaped both HIV and the hepatitis viruses, or acquired just one type of infection. Many of the latter group were, however, afflicted by serious illnesses, often fatal, at the time of transfusion; therefore, studying their subsequent course has generally not provided the depth of insight into HIV that the larger hemophilia patient cohorts have provided.

## Treatment Approaches

Except in the small number of HIV-infected subjects (approximately 2–5% ) who contain the HIV virus at very low levels, generally less than 1000 RNA copies/ml, and in whom CD4 T cell decline is slow or absent, relentless decline in immune competence is the norm, with a rate of decline correlated with HIV RNA viral load, irrespective of the mode of acquisition of the virus.<sup>20,25</sup> By contrast, those taking up treatment with antiretrovirals experienced dramatic immune reconstitution, and a corresponding improvement in prognosis, when the multi-agent HAART regimens were used.<sup>26</sup>

Fortunately, the principles of therapy for HIV in transfusion-acquired cases are broadly the same as those in the sexually acquired cases. A note of caution is that the newest agents targeting the HIV integrase enzyme, or co-receptor binding, were not specifically trialed in populations with congenital coagulopathies, such as hemophilia, hemoglobinopathies, or hemolytic diseases. Close scrutiny of post-marketing adverse event reports may reveal concerns regarding administration of specific new agents in future. Conversely, product warnings may provoke an overly pessimistic view of the likely side effect profile in these populations. On balance, careful planning of regimens is vital, and enhanced surveillance for adverse metabolic, hepatic, and bleeding side effects is required, but the need for treatment can be compelling, and often justifies proceeding with use of new agents, albeit cautiously. Some specific treatment issues warrant special consideration as listed in Table 88.1.

### BLEEDING

For patients with congenital bleeding disorders who require cART, it is important to establish whether the intended combination

**Table 88.1:** Treatment Considerations in Medically Acquired HIV Cases

1. Bleeding
2. Hypotension/risk of falls
3. Seizures
4. Anemia
5. Thrombocytopenia
6. Liver function
7. Induction of inhibitors
8. Induction of Immune Reconstitution Syndrome (IRS) involving hepatitis C and hepatitis B
9. Arthropathy and arthritis
10. Pre-existing bone demineralization
11. Unreliability of certain clinical and laboratory indicators
12. Fertility/heterosexual issues
13. Pain management drug interactions and use of NSAIDs
14. Vaccination
15. Surgery

has the potential to cause adverse effects on platelet function. For example, a number of reports have pointed to increased bleeding risk in patients with hemophilia taking Tipranavir, a modern protease inhibitor, which has also been reported to impact adversely on liver function in some patients. An observed effect of Tipranavir on platelet activation may be an explanation.<sup>27</sup> Careful monitoring can only partially offset idiosyncratic risks from antiviral therapies.

### HYPOTENSION AND RISK OF FALLS

HIV frequently causes subtle impairment of motor function, ranging from features seen in mild neurocognitive disorders to severe forms usually with HIV-associated dementia and cerebral atrophy on MRI examination of the brain.<sup>28</sup> Neurocognitive disorders can become the dominant determinant of HIV prognosis in those affected. The progression from minor abnormalities to the fully established manifestations of HIV-associated severe neurocognitive damage is usually slow and its progression appears to be slowed by antiretroviral therapy, though some cases progress despite cART.<sup>29</sup> Dramatic improvements in cognition after commencement of antiretroviral therapy have been documented in many individual case reports and larger retrospective analyses.<sup>30</sup> A minority of patients with hemophilia and HIV have experienced prior intracerebral bleeding with residual encephalomalacia, with its physical, neurocognitive, and seizure-triggering consequences. Fortunately, HIV-associated neurocognitive disorders are not overtly more prevalent in those infected with HIV in childhood and adolescence, but studies on these issues are sparse, as prior traumatic cerebral damage and the consequences of hemophilic arthropathy on balance and gait greatly complicate neuropsychometric studies and assessment of motor function.

In the management of HIV in patients with hemophilia and those with thrombocytopenia particular attention needs to be paid to ensure that the therapy of HIV and its complications do not produce hypotension or impair coordination leading to falls. This relates particularly to avoidance of overly aggressive management of diabetes/insulin resistance in people receiving cART.

## SEIZURES

Seizures are increased in people with HIV infection, and thus are a serious risk for hemophiliacs and thrombocytopenic patients with HIV, as seizures cause an increased risk of trauma and intracerebral bleeding. Conversely, the development of new seizures in a patient with hemophilia should prompt urgent assessment regarding the possibility of a primary intracerebral hemorrhage. A significant number of patients, particularly those who lived with hemophilia prior to modern therapies, have cerebral scarring, from previous intracerebral bleeding episodes, which may provoke seizure activity. Seizure recurrence should be minimized by anti-epileptics in hemophilia patients who have experienced even a single seizure. Prophylactic anticonvulsants are generally not recommended prior to a first seizure.

## ANEMIA

Establishing the cause of anemia in patients with HIV is often complex and laborious due to:

- (a) dyserythropoiesis due to HIV
- (b) the tendency for macrocytosis in patients receiving some of the nucleoside analogues (in particular Zidovudine)
- (c) altered vitamin needs
- (d) HIV associated risk of neoplasia

The high frequency of neoplasia, including gastrointestinal lymphoma, is seen across all modes of HIV acquisition. Anemia should be investigated when it occurs. The development of hemolysis in a patient with HIV should prompt consideration of the possibility of an occult lymphoproliferative disorder. Autoimmune hemolysis in HIV without underlying malignancy is surprisingly uncommon. Many patients with hemophilia or transfusion acquired HIV are also hepatitis C infected, and may need treatment with Interferon and Ribavirin. The latter can be associated with hemolysis and non-hemolytic anemia.

- (e) toxic hemolysis

In countries with a high prevalence of G6PD deficiency, toxic hemolysis is high on the list of differential diagnoses, and the choice of agents for prophylaxis of *Pneumocystis pneumonia* needs to take this into account. Atovaquone is increasingly finding a role in this setting as it does not carry a significant risk of inducing hemolysis.

## THROMBOCYTOPENIA

Thrombocytopenia in HIV is often multifactorial, and even more so in those with pre-existing hematological disorders. Those cases with an autoimmune basis or those resulting from bone marrow dysplasia generally improve with cART. Immune-mediated severe cases may require treatment with intravenous immunoglobulin, steroids, or occasionally splenectomy which may lead to interference with the ability to monitor the course of HIV due to its elevating effect on CD4 T cells.

Thrombocytopenia in combination with hemophilia and HIV is a particularly threatening situation. The platelet count thresholds for intervention with treatment for thrombocytopenia which apply in non-hemophiliacs, may need to be modified for those with severe factor VIII or factor IX deficiency, particularly if there is concurrent hepatitis C infection further impairing production of other coagulation factors produced by the liver.<sup>31</sup>

## LIVER FUNCTION ABNORMALITIES

The development of abnormal liver function tests in patients with transfusional HIV raises a long list of differential diagnoses. Determining the likely cause requires knowledge about prior vaccination status for hepatitis B and hepatitis A, as both these agents remain as potential blood transmissible, vaccine preventable risks to non-immune individuals. Hepatitis A lacks a lipid coat and therefore is not inactivated by solvent/detergent treatment of coagulation factors. However, the major cause of liver dysfunction in transfusion-acquired HIV is co-infection and activation of either or both hepatitis C and hepatitis B. Most cohorts of blood product recipients with HIV have shown that those who survived the first decade of HIV infection suffered accelerated hepatic damage from hepatitis C or hepatitis B in later years; furthermore, in many cases transaminases have not been significantly elevated during the slow development of cirrhosis. A small but important group of patients have been triply infected with hepatitis B, hepatitis C, and HIV,<sup>32</sup> and their course, if not adequately treated for hepatitis, is particularly problematic. Even those whose hepatitis virus has led to virus induced compensated cirrhosis and who do not have hemophilia experience mortality in excess of 5% per year if HIV infection is present.

Immune recovery with cART is sufficiently robust in many cases to allow safe and effective concurrent treatment of HIV and hepatitis viruses with cART and ribavirin/PEGylated interferon, respectively. Many centers have now reported comparable outcomes in hepatitis C eradication in long standing transfusion acquired HIV/hepatitis C co-infected cases as in a comparable population of patients dually infected through intravenous drug use,<sup>33</sup> but in both groups responses to therapy are inferior to hepatitis C mono-infected subjects with matched genotypes. Biomarker predictors of response to therapy, such as IL28 polymorphisms and levels of pre-treatment IP10, are increasingly being studied in hepatitis C infected subjects; if they or similar markers prove applicable in HIV/hepatitis C co-infection, patient selection for treatment will be greatly facilitated.

In general, hepatitis C in medically acquired co-infection should be treated with standard approaches for HIV/hepatitis C co-infected patients, mindful particularly of thrombocytopenia as a potential complication during interferon therapy.<sup>23</sup> The injections of PEGylated Interferon are generally well tolerated with only minimal bruising, and hemophiliacs do not usually require any supplemental coagulation factor concentrates. A number of studies, including a meta-analysis, have shown superiority of PEGylated Interferon 2-alpha over PEGylated interferon 2-beta in mono-infected patients, though a formal comparison has not



been made with an HIV-hepatitis C co-infected patient cohort such as hemophiliacs.<sup>34–36</sup>

Despite an inferior 5-year survival in HCV and HIV co-infected recipients of liver transplants when compared to HIV-negative hepatitis C infected subjects, worldwide there have been a number of liver transplantations performed for chronic viral hepatitis complicated by cirrhosis or malignancy. Although liver transplant may also provide a lifelong cure of the hemophilia if successfully grafted, infection of the transplanted orthotopic liver with the recipient's hepatitis virus is likely to follow even when vigorous attempts to prevent reinfection are undertaken. Immune reconstitution may provoke a serious flare up in active hepatitis B or hepatitis C, to the point of liver failure developing if hepatitis virus expression in the liver is active during weaning of immunosuppression or immunological reconstitution under the influence of cART. Consequently, those with co-infection by HIV and hepatitis C or HIV and hepatitis B need to be closely monitored during therapy for HIV. A number of studies have shown a high life-time risk of developing cholestatic complications during antiretroviral therapy in transfusion related co-infected patients. These should be managed similarly to other co-infected patients with cholestasis. New agents currently in advanced stages of clinical trials, directed at the hepatitis C protease, show great promise, and have the potential to further improve the success rate of hepatitis C treatment in the HIV/hepatitis C co-infected.<sup>37</sup>

## INDUCTION OF ANTIBODY INHIBITORS TO COAGULATION FACTORS

Initially there were concerns that the high frequency of autoimmune disease in patients with HIV might lead to an increased frequency of development of antibody-mediated inhibitors of coagulation pathway components. Fortunately, this has not happened, and in general, levels of clinically significant inhibitors have not been increased in people with HIV without pre-existing coagulation disorders, nor in those receiving either donor derived, or recombinant factor VIII pharmaceuticals, as treatment for hemophilia. However, patients receiving antiretroviral therapy occasionally develop inhibitors to coagulation, and some reports have viewed this as a manifestation of immune reconstitution syndrome (IRS).<sup>38</sup> Modern approaches involving tolerizing exposure to high-dose coagulation factor, immunosuppression, and cytotoxics to treat antibodies behaving as functional inhibitors, are problematic in HIV, as they damage T cell function, and even use of anti-B cell therapy in HIV adds additional immunosuppression to an already damaged immune system. Nonetheless, serious bleeding due to coagulation inhibitors may require cytotoxic therapy, rituximab (anti-B cell), corticosteroids and other immunosuppressants. Immunoabsorption techniques to remove immunoglobulins have also been reported to be of value in this setting, without the negative consequence on the integrity of the immune system, but they are short term in effect, and need to be supplemented by therapy directed at the underlying autoimmune process; other approaches have utilized coagulation

factors downstream in the coagulation cascade as pharmaceuticals to bypass proximal pathway deficiencies.<sup>39</sup>

## ARTHROPATHY AND ARTHRITIS

Hemophilic arthropathy, and the need for joint replacement for pain relief and to facilitate improved mobility, were fundamental drivers for the high rates of usage of factor VIII concentrates and factor IX concentrates in the early 1980s. When the available clotting factors were recognized to be unsafe, utilization of coagulation factors and surgery rates in hemophilia significantly decreased and have persisted to some extent in recent years in many countries, especially those without access to recombinant coagulation factors. Many patients remain reluctant to undergo high level exposure to coagulation products except in emergency situations. Hemophilic joints are prone to secondary infection both after instrumentation, and from hematogenous spread of bacteria. Early series revealed that salmonella was not uncommon as the causative agent in septic arthritis in HIV infection.<sup>40</sup> Treatment needs to be empiric pending culture, but other organisms found not infrequently include staphylococci, respiratory tract organisms, and gram-negative bacteria.

The development of a septic joint in a patient with hemophilia and HIV should prompt urgent aspiration and bacteriological studies, as the infecting organisms are potentially diverse. In practice, it is generally relatively easy to distinguish by history and examination acute hemophilic hemarthrosis from mechanical injury or sepsis, but acute polyarthritis poses a dilemma, as bacteremic seeding to already damaged joints and/or reactive arthritis may be indistinguishable without joint fluid analysis and culture.

## PRE-EXISTING BONE DEMINERALIZATION

Hemophilic arthropathy often results in wasting of muscles proximal and distal to the involved joints and secondary disuse and further joint injury may follow. Thus is set in train a pathway to non-generalized osteoporosis not uncommonly seen as demineralization of hemophilic patients' bones.<sup>41</sup> Those receiving cART are also susceptible to treatment-mediated further reductions in bone density, associated with low vitamin D levels in some cases. Bone mineral density studies are complex to interpret in those with hemophilic arthropathy, but nonetheless are worthwhile. Frequently, upper limb bone density is more suitable for assessment than hip and femoral density. Supplemental treatment with various anti-resorptive agents, bisphosphonates, calcium, vitamin D, and exercise programs may all have a place in this setting, but at present consensus is lacking as to the appropriate interventions to best deal with HIV-associated osteopenia.

## INTERFERENCE WITH CLINICAL AND LABORATORY TESTS

Hemophilia due to factor VIII or factor IX deficiency results in impaired coagulation *in vitro* as well as *in vivo*, and achieving "clean" serum samples is sometimes problematic with fibrinogen bands commonly present in preparations intended

to be purely serum. This can complicate the interpretation of electrophoretograms and has occasionally led to a misdiagnosis of paraproteinemia. Other clinical tests that may be adversely impacted by hemophilia include tests for the presence of hematuria; not infrequently urinary bleeding is the result of coagulopathy rather than underlying urinary tract pathology.

## FERTILITY ISSUES

Many of the world's surviving patients with HIV acquired from transfusion or coagulation factors are currently in fertile age groups. The genetics of hemophilia have resulted in the bulk of symptomatic cases being male, though occasional female carriers of X-linked genetic disorders are partially at risk. Symptomatic female carriers of X-linked coagulopathic disorders may have acquired HIV from transfusion of coagulation factors or blood, usually in the context of peri-operative treatment. Irrespective of the sex of the HIV-positive person, fertility issues abound in the management of people with HIV.<sup>42</sup> Assisted reproduction techniques are widely used to minimize the risk of transmission to a seronegative woman from a seropositive male. The converse is a much easier situation for the couple, wherein mechanical placement of sperm in the female genital tract at ovulation will often be sufficient to allow conception. HIV, or the therapy for it, may also impact on the efficacy of oral contraceptives. Most experienced practitioners dealing with medically acquired HIV recognize that fertility management forms an important part of the holistic care of people with HIV and their partners.

## PAIN MANAGEMENT AND DRUG INTERACTIONS

Those with a long history of painful bleeding into muscle and joints, sometimes repeatedly over many decades, have often acquired high pain tolerance. Nonetheless, a significant number of hemophilia patients require daily non-steroidal anti-inflammatory drugs to manage chronic arthritis and other orthopedic complications of their past hemarthroses. These agents have their own problems associated with platelet function but are nonetheless often necessary components of the pain management strategy. Opiates may be required for analgesia and supplementing background analgesia for acute injuries can be problematic. Co-existence of liver disease always needs to be kept in mind in people with HIV from transfusion, and the impact of cirrhosis on opiate metabolism is an important consideration. Serum transaminase levels are a poor guide to severity of underlying hepatitis virus-induced liver disease in HIV-infected subjects, so caution with opiate dosages is prudent in all those with a past history of hepatitis C or hepatitis B, whether or not they are currently viremic.

## VACCINATION

HIV-infection impairs vaccine responses to protein and carbohydrate antigens, and generally live vaccines are contraindicated in HIV-infected subjects outside of clinical trials. As the risk of acquiring hepatitis A from blood products is not

trivial in many countries, and as hepatitis A is not inactivated by detergent treatment of coagulation products, non-immune subjects with HIV should be vaccinated with hepatitis A vaccines. For poor responders, such as those with HIV, boosting beyond two doses may be necessary. Should hepatitis B serology not show prior exposure then vaccination with recombinant hepatitis B surface antigen is also recommended. Extended individualized schedules of vaccination and/or higher dose of antigen may be needed to achieve protective levels of antibody to immunogens in HIV positive people of all ages.<sup>43</sup>

## SURGERY

Many of those with medically acquired HIV will require surgery at some stage, for incidental conditions, or those conditions related to their underlying need for blood products or tissues. With modern hematological support major orthopedic surgery, including joint replacement, open heart surgery, vascular surgery and life saving cancer surgery, can all be safely conducted in appropriately experienced centers. Rigorous attention to hemostasis, prevention of nosocomial infection, and care in avoiding unwanted drug interactions, particularly those related to protease inhibitor use and cytochrome P4503A4 inhibition, are all essential components of surgical planning. Some patients are reluctant to have further exposure to blood products, so issues of adequately informed consent must be fully addressed. For all these reasons it is not uncommon for surgery to be delayed, with negative consequences. Experienced multidisciplinary teams have much to offer in the management of surgical patients with HIV, and this applies particularly to those with pre-existing complex medical issues; consequently patient transfer to a tertiary setting is often worth the inconvenience and delay.

## Ongoing Risk Minimization

Strenuous efforts have been mounted worldwide to secure the safety of blood products and develop alternatives to donor-derived materials. Currently, recombinant Factor VIII is increasingly being used for the treatment of hemophilia due to Factor VIII deficiency, providing a level of safety not previously achievable with donor-derived products.<sup>13</sup> Efforts to treat hemophilia by gene therapy offer the prospect of non-infusional treatments in the future, but there are many obstacles to overcome prior to successful gene therapy of a potentially immunogenic protein such as Factor IX.<sup>44</sup> In many countries the cost of recombinant coagulation factors is prohibitive and plasma or plasma fractions such as cryoprecipitate are still in widespread use, with ongoing need to ensure donated product safety. The future safety of donor-derived materials depends on six risk reduction measures, some of which are not suitable for fresh blood and organ protection:

1. Donor selection
2. Laboratory screening by serological and NAT technology
3. Retesting of donors of storeable products at a later date prior to product release

4. Product processing to inactivate viruses
5. Recipient screening and lookback assessment with case finding of infected donors
6. Scrupulous attention to maintaining sterility of equipment used for blood and plasma collection and avoiding iatrogenic donor infection from shared donation collection tubing.

Internationally, however, there remain significant variations in strategies in place in all the above domains, a situation likely to persist for many years to come (Fig. 88.2).

## DONOR SELECTION

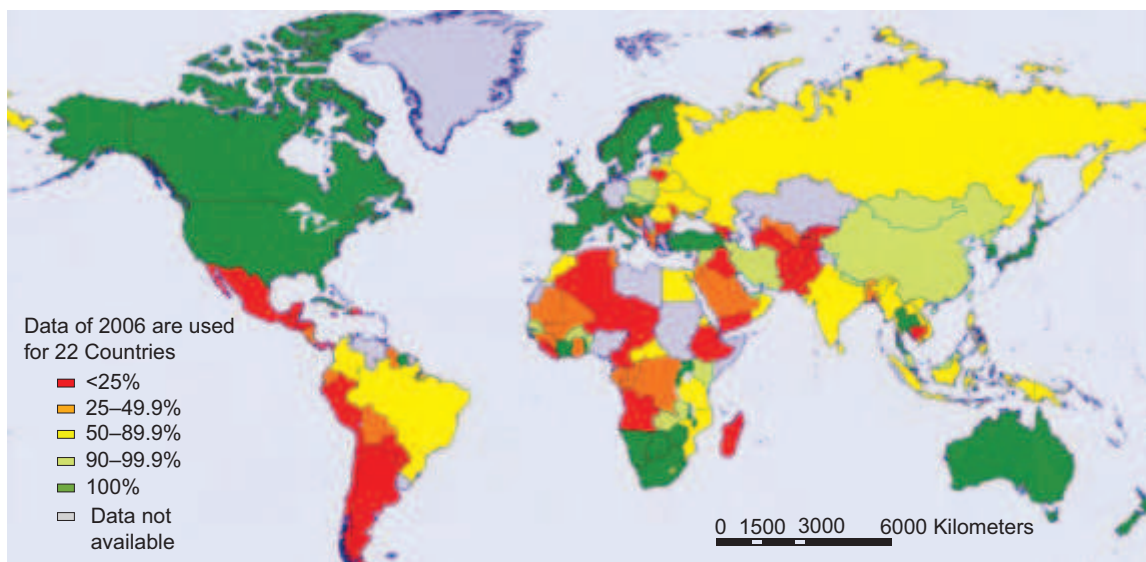
Early attempts to protect the integrity of the blood supply involved rigorous donor selection based on questionnaire responses that included travel and behavior declarations, aimed principally at excluding homosexual male donors. Those potential donors who were perceived on the basis of geographical, medical, or behavioral characteristics to be at high risk of harboring HIV were and continue to be excluded from the donor pool.<sup>45</sup> Detailed interview and risk assessments with surrogate testing for concurrent hepatitis and sexually transmitted infections were carried out in some jurisdictions, stemming from the earlier work on recognition of non-A, non-B hepatitis infections, (subsequently shown to be mainly hepatitis C). These various measures are generally believed to have significantly improved blood safety even prior to HIV serology being available. Recent sophisticated analyses of transfusion-related risk include one study from Brazil where despite use of antibody screening in the region of Santa Catarina, Brazil,<sup>46</sup> the high rates of incident HIV result in calculated risk of blood borne virus (BBV) well above those considered acceptable in most jurisdictions. Undue reliance on serological screening in countries with even higher rates of newly

acquired HIV in heterosexuals continually expands the numbers of transfusion transmitted infections.

For travelers who are returning to low HIV prevalence countries from high-prevalence countries, it is particularly important for their regular practitioner to seek information about any contact with biological products or invasive procedures while away. Travel and medical histories need to be comprehensive and include information about batch numbers if processed products were involved. The international hemovigilance situation is rapidly changing; this reflects changes in true incidence rates, and to an indeterminate degree, the spread of HIV to traditionally low-risk donors such as self-perceived monogamous heterosexuals. The analysis of serology from hemophiliac cohorts from developed countries in the early 1980s cast doubt upon the widely held view that plasma and blood products sourced from volunteer donors was significantly safer than commercially sourced plasma.<sup>6,47</sup> Furthermore, many large contaminated batches of freeze-dried coagulation factors were unwittingly sold world-wide, and few countries escaped some exposure of their hemophilia patients to HIV prior to introduction of heat-treated products, even those with very low background population prevalence of HIV, such as Japan.<sup>48</sup> In recent decades, international cross jurisdiction movement of plasma has further grown and necessitates constant vigilance in donor testing at source. Ensuring integrity of the blood supply at collection has allowed dismantling of some of the barriers to plasma movement across borders.

## SCREENING FOR HIV AND OTHER BBVS BY NAT

Best practice in donor screening is the use of serological screening for HIV-1/2 antibody using high-sensitivity assays with greater than 99% sensitivity for established infection, and a supplementary technique to detect antibody negative viremic subjects, by HIV



**Fig. 88.2:** Percentage of voluntary unpaid blood donation 2007. *Source:* WHO.



antigen detection, or HIV gene sequence detection with NAT methods. However, the reality is that in many jurisdictions hemovigilance for HIV is constrained by the cost implications of enhanced screening, and extends only to antibody screening, even in countries with high prevalence/incidence rates in the general population. That strategy will inevitably result in some transmissions from seroconverting or pre-seroconverting donors unaware, (or in denial), of their risk. The 2008, United Nations General Assembly Special Session indicators of progress in the battle against HIV include indicator number 3, the percentage of donated units screened in a quality assured manner.<sup>49</sup> Setting indicators such as these allows a scorecard approach to the assessment of progress in achieving enhanced blood safety. On the other hand, commercial plasma fractionation is a large industry and a significant proportion of plasma collections still derive from paid plasma donors.

### RETESTING OF DONORS

For donors of plasma, it is possible to quarantine the product until the donor has been retested at a later stage. Similar strategies have been used for semen donors in *in vitro* fertilization programs and for tissue banking. In most blood banks handling blood products of short shelf-life, logistic considerations prevent the widespread use of a donor retest strategy, except for regular donors in plasmapheresis or cell apheresis programs.

### INACTIVATION OF VIRUSES

Although prolonged heat treatment can inactivate HIV, neither freezing nor lyophilization impacts significantly on the viability of HIV in contaminated blood products. Heat treatment inactivation and/or solvent-detergent exposure during manufacture for lyophilized coagulation factors was introduced in a piecemeal fashion<sup>48</sup> across blood banking jurisdictions during the early and mid 1980s. The Scottish National Blood Transfusion Service was the first to develop a means of treating lyophilized coagulation products at 68°C in 1984, and made the technology available to other blood banks and plasma fractionators, enabling Australia to be the second jurisdiction with heated licensed products in May 1985. Thereafter, heated lyophilized products or solvent/detergent treated products were widely used by the end of 1985, and almost universally used in developed countries by early 1986, marking a time after which lyophilized heat treated or solvent/detergent treated coagulation factors ceased to be a risk for HIV transmission. Subsequently a variety of chemical and physical viral inactivation processes,<sup>50</sup> despite their lack of efficacy against all potential BBVs, have become the standard approach to enhancing safety of manufactured coagulation factors, supplemented in many cases by additional heating. Most licensed solvent/detergent processes rely on tri (n-butyl) phosphate (TNBP) as the solvent moiety, and a variety of detergents are the other component of the processes, most of which are proprietary.

### POST-RELEASE RECIPIENT SCREENING

Confidence in the safety of the currently available blood products has led to the view that routine post transfusion screening for newly acquired BBVs is not warranted in the absence of an index case of transfusion related viral infection or the identification of an infected donor from screening. Nonetheless, many centers continue to test frequently infused and transfused recipients for BBVs, with a low yield of positive diagnoses, and the generation of considerable anxiety on the part of recipients.

### MAINTAINING STERILITY OF EQUIPMENT USED IN BLOOD AND PLASMA COLLECTION

Many reports during the 1980s and into the 1990s pointed to increased rates of chronic viral infection in paid donors in plasmapheresis programs.<sup>51</sup> While some countries have attributed this to the plasmapheresis program serving as a source of income for intravenous drug users, some outbreaks, such as one in Mexico, were clearly the consequence of iatrogenic transmission of viruses to donors during plasmapheresis.<sup>52</sup> International standards call for single-use equipment, sterile swabs, and wherever feasible, non-reuseable bedside equipment, as the means of minimizing the potential for donors themselves to become infected during donation, the consequence of which is contamination of future donations.

### Cost-Benefit Considerations

At present, in low HIV-prevalence countries, enhanced hemovigilance with individual sample NAT testing superimposed on single sample serology, has a high cost-to-benefit ratio but the community rightly has expectations that the blood supply is as safe as humanly possible, thereby justifying the costs involved.<sup>53,54</sup> Most high-income countries have moved to high-throughput high speed NAT of all donated samples over the last decade, and other enhanced hemovigilance steps as outlined above. In such countries these protocols of donor selection and testing should make newly acquired HIV and other viruses from blood transfusion or blood products extremely uncommon in the future.

### Other Future Issues

Other future issues for transfusion recipients with HIV are numerous. Significant numbers of infants were infected in the early 1980s and many of these, now adults, have HIV-negative heterosexual partners, and are currently seeking to have children. Assisted reproduction services are not widely available to assist such couples and those caring for them require local knowledge of available services and knowledge of legal and financing regulations that are pertinent. At the other end of the age spectrum, long-term

survivors of the wave of HIV infection of the early 1980s include a subgroup in which ageing with its attendant co-morbidities provides additional management complexities. Complications of previous intracerebral bleeding can complicate interpretation of neurocognitive decline of age and false diagnosis of HIV related neurocognitive decline is an ever-present diagnostic hazard to the clinician.

The human stories behind the statistics of transfusional HIV have much to teach the student of public health. Moralistic thinking clouded scientific debate in the early years of the AIDS epidemic, and discrimination abounded in most, if not all countries. People living with HIV acquired from medical interventions have often lived through periods of extreme hardship, fear, and physical illness all attributable to the HIV virus. Laws, charitable institutions, and healthcare funding models needed to adapt to the reality of HIV and it was often in the context of dealing with the needs of transfusion cases that discriminatory practices were overturned. The survivors still bear the scars of the time prior to the recognition of their plight and many still harbor a fear of the “next virus,” a fear that is in no way irrational as the waves of other blood borne infections have been confronted. Hemophiliacs worldwide have needed to be vaccinated against hepatitis A because of its resistance to detergent and heat; they have been assessed for prion-related disease and have been aware of the threats of west Nile virus and parvovirus in the US and Europe, and of other microbes so far undiscovered. The lessons of the need for hemovigilance have been learnt at all levels of healthcare but most poignantly by those who have cared for those infected by transfusional HIV and the other BBVs.

Courts have varied in their judgment of the extent to which those managing the blood supply and its downstream processing have been misled, negligent or worse.<sup>55</sup> Healthcare workers are constantly reminded of the need to treat blood products as potentially contaminated, and harboring any number of threats to the recipient. At the present time, as a result of the efforts to secure the blood supply, the risk of an adverse outcome from blood transfusion is far greater from misidentification, transfusion incompatibilities, and bacterial infection, than it is from infection with BBVs. Efforts need to continue, both at a regulatory level<sup>56</sup> and in basic science laboratories, to further lower those risks which are still very high in many low income countries,<sup>57</sup> and to maximize the health of those who have already been infected.

Just as the last two decades delivered huge advances stemming from molecular biology, in particular, widespread availability of recombinant coagulation factors such as Factor VIII thereby eliminating reliance on donor-derived Factor VIII, it is conceivable that the next decade will provide advances in gene therapy such that people who have acquired their HIV infection from infused blood are protected by cells armed by gene therapy to resist HIV.<sup>58</sup> Finally, the need for many forms

of donor blood product exposure may be reduced by somatic cell gene therapy which is particularly suitable for treatment of congenital coagulation disorders.<sup>59</sup>

### Summary

In the half-decade preceding the discovery in 1983 that acquired immune deficiency syndrome (AIDS) was caused by a blood-borne retrovirus, which was also readily transmitted sexually, HIV was frequently an unsuspected contaminant of donated blood and manufactured therapeutic products of human origin. Infected recipients began developing AIDS as early as 1982 in the US, and soon afterwards cases were recognized in many other countries. Despite the high mortality of HIV disease in the time prior to the use of effective combination antiretroviral therapy (cART) in the mid 1990s, many people infected with HIV by blood products nonetheless survived the many intervening years. In many countries, long-term HIV infected blood product recipients now are predominant among living medically acquired HIV cases and number many tens of thousands worldwide.

Most countries have introduced sophisticated screening tests of blood and tissues as part of enhanced hemovigilance for transmissible viruses; however, even in those with implementation of viral nucleic acid testing (NAT) of donations occasional new HIV infections still occur in recipients. Newly acquired transfusion and tissue transplant related HIV infections are generally the consequence of the limited sensitivity of HIV antibody tests in detecting the infection within the first few weeks after exposure, as well as the limited success in preventing high-risk donors from donating.

The principles of management of medically acquired HIV are in most respects similar to those applicable to sexually acquired infection, as both modes of acquisition have very similar prognosis and respond to antivirals comparably. The complexity of management is, however, increased by the common presence of pre-existing co-morbidities and transfusion-acquired co-infection with chronic hepatitis viruses. Medical conditions such as hemarthroses, muscle damage, and cerebral injury from prior bleeding episodes further complicate management in hemophiliacs. Enthusiasm for the use of the most recently available antiretroviral agents is tempered in those with hematological diseases by concerns about the potential for adverse effects on coagulation and homeostasis. Integrase inhibitors and cellular CCR5 co-receptors binders are yet to have their long-term safety fully determined in coagulopathy patients, in others requiring frequent blood products, and in those with co-existing chronic hepatitis. Thus there is a need for ongoing evaluation of the safety of new antivirals in subjects with hemophilia and hemoglobinopathies, during the early and later phases of drug development, and in post-marketing monitoring. Ultimately, the lifespan of people with medically acquired HIV living in the post cART era is likely to be determined principally by the outcome of co-morbid conditions, co-infections with chronic hepatitis viruses, and the course of the underlying disease that originally prompted transfusion of blood.

- HIV infection from contaminated donor blood exposure may still occur despite screening.
- Most donor-derived blood cell-free products undergo viral inactivation steps in manufacture to minimize the risk of viral transmission.
- Implementation of quality assured standards for virus testing in global blood banking is a high priority.
- Hepatitis virus co-infection with hepatitis C, hepatitis B or both may impact on decisions in timing of initiation of therapy for HIV and the choice of agents in cART
- Co-morbidities in hemophiliacs patients warrant consideration in planning HIV therapy.

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# 89

## HIV in Injection and Other Drug Users

Jaimie P. Meyer • Frederick L. Altice

### Introduction

Injection drug use (IDU) and HIV are pervasive overlapping epidemics<sup>1-3</sup> with a vast array of social and health consequences at both the individual and societal levels. IDU is particularly important in the HIV epidemic, not only as a vehicle of viral transmission among IDUs but also serves as a bridge from IDUs to their sexual partners and to others within broader social networks.<sup>4</sup> For the clinician, it is imperative to recognize drug use in HIV-infected patients to effectively screen and vaccinate for concurrent related infections, monitor for end-organ complications, and offer treatment for substance abuse, HIV, and other co-morbid conditions. Of particular importance to the HIV clinician are the special clinical features of HIV disease in drug-dependent patients, the treatment of HIV disease in this population, the special challenges in providing care to drug users, and the treatment of drug dependence itself. Engaging HIV-infected injection drug users (HIDUs) in care and initiating antiretroviral therapy (ART) is of the utmost importance. ART, when prescribed and adherence is optimized, improves health outcomes for HIV and many of its co-morbid conditions, including tuberculosis, viral hepatitis, and renal and cardiovascular disease.<sup>2</sup> On a public health level, addressing drug use in people living with HIV/AIDS (PLWHA) is critical for secondary HIV, hepatitis C, and tuberculosis prevention efforts. This chapter offers a broad perspective on concurrent HIV infection and injection drug use, including an overview of substance abuse and evidence-based treatment options, other common co-morbidities in this population, and public health strategies to address these issues.

### Healthcare Disparities for HIV-Infected Drug Users

Highly active antiretroviral therapy (HAART) has greatly benefitted PLWHA, including decreased morbidity, mortality,<sup>5</sup> emergency department use,<sup>6</sup> and hospitalization,<sup>7</sup> and has been demonstrated to be cost-effective<sup>8</sup> and improves quality of life.<sup>9</sup> Despite the widespread availability of antiretroviral medications

in resource-rich settings, IDUs have derived less benefit than other populations.<sup>2,10,11</sup> The reasons for inequality are multifactorial and include differences in access to and prescription of HAART. In low- and middle-income countries, HIDUs are less likely to receive ART than PLWHA who do not use drugs.<sup>12</sup> Even in industrialized countries, HAART is often withheld from IDUs, amounting to significant violations of basic human rights.<sup>13</sup> Potential barriers to HIV and substance abuse treatment include social marginalization, fear of criminal sanctions, costs, and incarceration.<sup>12</sup>

Drug-dependent people living with HIV experience ongoing discrimination. In many societies worldwide, both HIV and illicit drug use are stigmatized such that either or both conditions are often cloaked in secrecy and may result in a lack of detection and treatment.<sup>14,15</sup> In some cultures, ongoing substance use is perceived as a self-inflicted disease resulting from personal moral failures.<sup>16</sup> Drug users are seen as having little social worth. Physicians may view drug users as manipulative, unmotivated, and undeserving of care,<sup>17</sup> in part because many HIV providers are poorly educated about drug dependence. In turn, many drug users are mistrustful of the healthcare system and harbor expectations that they will be treated punitively.<sup>18-20</sup> As a result of these prevailing misconceptions, HIDUs are often hidden by circumstances and/or choice from mainstream medical care.

Providing clinical care for drug users with HIV is often challenging and stressful for clinicians and other healthcare workers because of the complex array of related medical, psychological, and social problems. Frequent underlying and untreated psychiatric disease, including personality disorders, often contribute to these difficulties. Substance misusers may also have increased difficulties with adherence to medications<sup>21-24</sup> which may be compounded by their underlying co-morbid diseases, increased side effects, and drug interactions. The idea that all drug users are non-compliant with HAART and thus risk development of drug resistance is a common misperception among healthcare providers. This myth has been discredited by scientific evidence.<sup>16</sup> Best predictors of HAART adherence in one recent meta-analysis of HIDUs were receiving opioid

substitution therapy and/or psychosocial support.<sup>25</sup> Treatment failures are more often the result of system-wide structural barriers to care.<sup>13</sup> Even when available, healthcare services are often constructed in ways that are difficult for many drug users to access. They are either absent from communities with high prevalence of drug use or do not accommodate the chaotic and sometimes unpredictable use of services characteristic of drug-using populations. Indeed, systems of integrated care for HIV-infected drug users are lacking.

## Overview and Management of Substance Use Disorders in People with HIV

A list of commonly used illicit drugs along with evidence-based treatments is presented in Table 89.1 and will be described in more detail in this section. For further information, please refer to the National Institute on Drug Abuse website ([www.drugabuse.gov/drugpages](http://www.drugabuse.gov/drugpages)) and that of the World Health Organization (WHO) ([www.who.int/substance\\_abuse](http://www.who.int/substance_abuse)).

**Table 89.1:** Common Legal and Illegal Drugs Consumed and Their Impact on HIV

Substances used	Common adverse clinical consequences of ingestion	Mode(s) of use	Impact on HIV	Evidence-based medication-assisted treatment(s)
Opioids (heroin, morphine, hydromorphone, codeine, poppy-straw)	Respiratory depression, coma, overdose; physical and psychological dependence	Injection; inhalation (smoked or sniffed), oral (synthetic only)	↓s access to and utilization of care; ↓d prescription of ART, ↓ adherence to ART	Methadone (oral); buprenorphine (sublingual); naltrexone (oral, injectable)
Cocaine (white powder, crack)	Agitation, hyperthermia, tachycardia, arrhythmia, hypertension, convulsions, cardiac and CNS disturbances, hallucinations, death, psychological dependence.	Injection; inhalation (smoked or sniffed)	↓s access to and utilization of care; ↓d prescription of ART; ↓d adherence to ART; ↑d sexual and drug risk behaviors	None
Benzodiazepines	CNS depression, sedation, ataxia, amnesia and coma; deaths are rare when benzodiazepines are taken alone; physical and psychological dependence are rapid and profound.	Injection; oral	Associated with ↑d sexual and drug risk behaviors; ↓d adherence to ART; ↑d sexually transmitted infections	Slow supervised taper and withdrawal required
<b>Club Drugs</b>				
Methamphetamine and amphetamine-group substances (AGS)		Injection; inhalation; per rectum	↓s access to and utilization of care; ↓d prescription of ART, ↓d adherence to ART; some ART ↑s risk of AGS overdose	None
3,4 methylenedioxy-methamphetamine (MDMA)	With overdose, serotonin syndrome, stimulant psychosis, and/or hypertensive crisis, cognitive and memory impairment, acute delirium, cardiac arrhythmias or infarction, coma; profound depression several days after use	Oral (tablet)	↓d adherence to ART on days of MDMA use	None
Ketamine	Hypertension, cardiac arrhythmias, cognitive impairment;	Injection, inhalation (sniffed or smoked)	Not known	None
Gamma hydroxybutyrate (GHB)	Oversedation, coma, death, seizures, hypotension and shock, psychosis and agitation.	Oral (liquid)	Not known, but likely similar to alcohol	None
Nitrates/nitrites (poppers)	Methemoglobinemia, hemolytic anemia especially those with G6PD deficiency, hypotension, cardiac arrhythmias	Inhalation (liquid)	Associated with ↑d HIV risk behaviors	None
Alcohol	CNS sedation, some malignancies, hepatic injury, dietary deficiencies, pancreatitis, gastritis, neuro-cognitive deficits	Oral	↑s hepatotoxicity; ↑s peripheral neuropathy; ↓s access to and utilization of care, ↓d prescription of ART, ↓d adherence to ART	Naltrexone (oral, depot injection); acamprosate; disulfiram

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↓/↑s, decreases/increases; ↓/↑d, decreased/increased.



The drugs most closely associated with HIV infection globally are heroin and cocaine, but amphetamine-group substance (AGS) use is an evolving problem.<sup>26</sup> Injection with shared contaminated needles, syringes, drug preparations, or other injection paraphernalia carry the greatest risk for HIV and other blood-borne infections transmission.<sup>27,28</sup> To transform substances from solid to liquid form suitable for injecting, one first heats the solid drug in a cooker or spoon. After it cools, the liquid is drawn up in a syringe through cotton to grossly filter out other debris. A needle is then attached and the drug is injected either intravenously (most commonly in the brachiocephalic veins of the antecubital fossa) or subcutaneously in a process known as “skin popping.” Often, unsterile injecting techniques are used. Injection paraphernalia may be shared and residual blood may be present in the equipment itself. As such, the processes of preparing and injecting drugs provide ample opportunities for microbial cross-contamination and viral transmission.

Non-injection drug use may also contribute to adverse outcomes in HIV-infected patients. Use of non-injection stimulants, such as cocaine and methamphetamine, is associated with increased HIV risk behaviors<sup>29,30</sup> and suboptimal adherence to HIV treatment.<sup>31</sup> Non-injection drugs also influence cellular immune responses and may interact with ART, potentially leading to increased incidence or severity of adverse events.<sup>32</sup> Non-injection drug and alcohol use increasingly facilitates HIV transmission, particularly among women, through its association with the exchange of sex for money or drugs.<sup>33</sup> Furthermore, the disinhibition that occurs with drug and alcohol intoxication is closely linked with risk-taking activities (including unprotected sex and needle-sharing), increasing the likelihood of HIV exposure and transmission.<sup>34</sup>

## COMMON DRUGS OF ABUSE

### Heroin

Heroin, the most widely used opioid, is a short-acting, semi-synthetic opiate produced from opium. It may be smoked, inhaled, or injected; peak heroin euphoria begins shortly after injection and lasts approximately 1 hour, followed by 1–4 hours of sedation. Withdrawal symptoms commence several hours later. As a consequence, most heroin-dependent individuals inject 2–4 times per day. Many heroin users will mediate the sedating effects of heroin by injecting a small amount of cocaine with heroin, a mixture known as a “speedball.” Unsterile methods of injection, unpredictable concentrations in street-derived samples, acute euphoria resulting in increased risk-taking, adulterants in the injection mixture, and the lifestyle necessary to procure drugs are responsible for the bulk of heroin-associated medical complications.<sup>35</sup>

### Cocaine

Among the stimulants, cocaine is most commonly used. Cocaine is available as a water-soluble hydrochloride salt that is either injected or taken by nasal inhalation (“snorted”). Although cocaine hydrochloride is destroyed by heat, it may be chemically converted to a free-base

(“crack”) cocaine, which can be smoked. Pulmonary absorption of “crack” is as rapid as intravenous injection of cocaine. Cocaine’s half-life is short, resulting in the need for frequent administration. Active cocaine users may inject or inhale cocaine as many as 20 times a day. Cocaine induces feelings of elation, omnipotence, and invincibility and invokes rapid development of psychological dependence. The most severe direct medical consequence of cocaine use is vasospasm, an idiosyncratic response that can result in myocardial infarction and cerebrovascular accidents in young persons without any evidence of vascular disease.<sup>35</sup>

### Benzodiazepines

Benzodiazepines, a class of sedative hypnotics, are sometimes injected after crushing the tablet formulation, often resulting in soft-tissue and vascular complications.<sup>36</sup> When combined with other drugs, benzodiazepine use is associated with decreased retention in drug treatment, increased HIV risk behaviors, fatal and non-fatal overdose, and increased mortality.<sup>37–39</sup> Like opioids, benzodiazepines cause both physical and psychological dependence and can result in dangerous complications associated with withdrawal.<sup>40</sup>

### Amphetamines

AGS are psychostimulants that include amphetamine, methamphetamine, and their derivatives.<sup>26</sup> AGS can be smoked, snorted, injected, or administered rectally. Like cocaine, ingestion produces stimulation and similar feelings of euphoria; AGS, however, have a longer duration of action than cocaine, with a half-life of 9–12 hours. Psychological dependence develops rapidly, as does tolerance, and escalation of dose and frequency is required. Because of this pharmacokinetic profile, AGS are often used in a sexual context to facilitate disinhibition and thus have been linked to high-risk sexual behavior and HIV transmission, especially among men who have sex with men.<sup>26,41</sup> For healthcare providers, recognition of AGS abuse in HIV-infected patients is critical. AGS and some antiretrovirals, including ritonavir and delavirdine, share a common metabolic pathway and co-administration has been linked to amphetamine overdose fatalities in several published case reports.<sup>30</sup>

### Alcohol

Alcohol use disorders (AUDs) are common among PLWHA, with an estimated prevalence of 8–41%,<sup>42–45</sup> In fact, AUDs are 2–4 times more common among PLWHA than among their uninfected peers.<sup>46</sup> Patterns of hazardous alcohol consumption are most prevalent in global regions with concentrated HIV epidemics, particularly in eastern and southern Africa.<sup>47</sup> Heavy alcohol use negatively acts synergistically with HIV in several ways, including increased HIV risk-taking behaviors<sup>48–50</sup> and thereby increased risk for transmission to others,<sup>51</sup> decreased retention in care,<sup>52</sup> poor adherence to ART,<sup>53,54</sup> decreased likelihood of HIV virologic suppression,<sup>11,55</sup> acceleration of cognitive decline,<sup>56</sup> acceleration of hepatic fibrosis in the setting of HCV co-infection,<sup>57</sup> and overall increased mortality.<sup>42,58</sup>

## MANAGEMENT OPTIONS FOR SUBSTANCE ABUSE

The World Health Organization (WHO) defines substance dependence as the psychological and/or biological need for alcohol or drugs in order to function or survive, a pattern that emerges only after repeated use. Substance abuse is defined as a maladaptive pattern of use that persists in spite of negative social, psychological, or physical consequences.<sup>59</sup> Together, abuse and dependence are grouped under a larger umbrella of substance use disorders (SUDs). A wide range of treatment options for SUDs exist and are best used in an integrated way that is tailored to the individual.

## Evidence-Based Medication Assisted Therapies

Medication-assisted therapies (MATs) use clinician-prescribed medication to reduce the negative consequences of drug use. MAT alone, or when coupled with brief counseling/education, can

result in impressive outcomes, improving the psychological and physiological disruptions that perpetuate the often unstable life of a drug-dependent person.<sup>60</sup> Available MATs for opioid and AUDs are listed in Table 89.2. There are no currently available evidence-based pharmacotherapies for cocaine or amphetamine abuse; counseling remains the only evidence-based treatment modality shown to decrease use of cocaine and methamphetamine.<sup>61,62</sup>

### MATs for Opioid Use Disorders

Medically supervised opiate withdrawal followed by intensive outpatient treatment may be a viable treatment option for users with relatively low addiction severity. These include short-term opiate users (less than 2 years), young adults, and non-injectors.<sup>63,64</sup> The withdrawal process involves a supervised gradual taper from opioids using methadone or buprenorphine.<sup>65</sup> Alternatively, medically supervised withdrawal may involve

**Table 89.2:** Available Medication-Assisted Treatments for Opioid and Alcohol Dependence

Medication	Type of dependence	Mechanism of action	Pharmacological properties	Adverse side effects	Substance abuse treatment outcomes	Impact on HIV	Other issues
Methadone (MET)	Opioid	Pure opioid $\mu$ -receptor agonist	Half-life 24–36 hrs. Ingested orally as tablet or liquid. Achieves steady state within 5 days	Tolerance to side effects usually develops; diaphoresis, constipation, and amenorrhea (menses usually return after 12–18 mo). Excessive dosing or when combined with alcohol may cause overdoses or death.	↓ relapse to illicit opioid use; ↓ number of days using illicit opioids; ↓ opioid and cocaine use after release from prison; ↓ criminal activity; ↑ employment; cost-effective	↓ injection and HIV transmission; ↑ retention in HIV care; effective supporter of directly administered ART (DAART); ↑ effectiveness of ART	No euphoria felt after being on stable methadone dose; doses of 30–60 mg daily will block opioid withdrawal symptoms, but this dosage seldom produces abstinence. Instead, higher doses in the 80–120 mg daily range are needed to ↓ opioid craving and ↓ illicit drug use. These higher doses are also associated with greater retention in treatment. Only administered in highly structured treatment settings with directly observed therapy.
Buprenorphine (BPN)	Opioid	Partial opioid $\mu$ -receptor agonist and partial $\kappa$ -receptor antagonist	Half-life 24–36 hrs. Administered sublingually. Slow dissociation from the $\mu$ -receptor allowing alternate-day dosing	Improved safety profile compared to methadone; unlikely to cause overdose or respiratory depression; higher binding affinity for the $\mu$ -receptor than heroin or methadone, therefore precipitates withdrawal in person still with opioids in their system.	↓ relapse to illicit opioid use; ↓ number of days using illicit opioids; ↓ opioid and cocaine use after release from prison; ↓ criminal activity; ↑ employment; cost-effective	↓ injection and HIV transmission; ↑ retention in HIV care; effective supporter of DAART; ↑ effectiveness of ART; ↑ retention on ART after release from prison	↓ likelihood for medication diversion and abuse potential compared to methadone; injection of BPN in opioid dependent persons precipitates withdrawal symptoms; may be given in less structured settings, including as part of integrated HIV care
Buprenorphine/naloxone	Opioid	Partial opioid $\mu$ -receptor agonist and partial $\kappa$ -receptor antagonist; naloxone is a short-acting $\mu$ -receptor but not orally bioavailable antagonist	Half-life 24–36 hrs. Administered sublingually. Slow dissociation from the $\mu$ -receptor allowing alternate-day dosing	Same as for buprenorphine; naloxone used to reduce likelihood for diversion and injection	Compared to high dose methadone, retention in treatment is lower	Same as for buprenorphine; when injected, likely results in more frequent injecting and increased risk for HIV transmission	Used to ↓ likelihood of illicit injection because coformulation with naloxone precipitates withdrawal symptoms in opioid dependent patients when used parenterally; injection frequency, however, may ↑ the frequency of injections

Medication	Type of dependence	Mechanism of action	Pharmacological properties	Adverse side effects	Substance abuse treatment outcomes	Impact on HIV	Other issues
Naltrexone	Opioid	Pure $\mu$ -receptor opioid antagonist.	Oral formulation dosing is daily or alternate-day dosing; Injectable formulation administered intramuscularly monthly (improves adherence)	Hepatotoxicity possible; has been administered safely in HCV-infected patients	Retention in treatment is lower than for MET or BPN, but may be considered in highly motivated patients.		Discourages opioid use by diminishing the pleasurable effect of and craving for opioids, and has demonstrated efficacy in highly motivated populations
Naltrexone	Alcohol	Blocks the pleasant and reinforcing effects of alcohol by preventing the stimulation of opioid receptors and the reduction of dopamine release in the ventral tegmental area (VTA)	Oral formulation dosing is daily or alternate-day dosing; Injectable formulation administered intramuscularly monthly (improves adherence)	Hepatotoxicity possible; has been administered safely in HCV-infected patients	Superior to behavioral counseling and acamprosate for treatment of AUDs in HIV uninfected persons. $\uparrow$ s time to relapse, $\downarrow$ s number of heavy drinking days	Not studied in HIV-infected subjects	
Acamprosate	Alcohol	Structural analog of the GABA neurotransmitter; normalizes glutamatergic neurotransmission; slow acting, may attenuate relapse in some	Orally dosed with two tablets three times per day; adherence may be problematic	Few adverse side effects	$\uparrow$ d abstinence confirmed in placebo-controlled trials, but no benefit in preventing relapse by itself or in combination with counseling.	Not studied in HIV-infected subjects	Less effective than naltrexone, equivalent to counseling, and superior to placebo for alcohol relapse prevention; approved by US FDA (2004) for relapse prevention in subjects who have already withdrawn from drinking
Disulfiram	Alcohol	Inhibits acetaldehyde dehydrogenase and causes accumulation of acetaldehyde when alcohol is consumed. This leads to painful symptoms such as facial flushing, dyspnea, nausea, vomiting, and headache, thereby discouraging relapse to alcohol consumption.	Orally dosed, half-life 24 hrs;	Nausea and vomiting if alcohol is ingested; hepatotoxicity	Not studied in HIV-infected subjects; should not be combined with Amprenavir (probable interaction) or Metronidazole (probable interaction)	Hepatotoxicity; Causes profound nausea and vomiting when alcohol is ingested	May be useful when combined with other interventions, including methadone when a patient is opioid-dependent

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$\downarrow/\uparrow$ s, decreases/increases;  $\downarrow/\uparrow$ d, decreased/increased.

abrupt discontinuation of opioids with management as needed of withdrawal symptoms. Although more symptomatically uncomfortable for patients and with demonstrated inferior outcomes, clonidine may be used to alleviate some symptoms of opioid withdrawal.<sup>65</sup>

Relapse to drug use among chronic opiate users exceeds 85% when patients undergo supervised opiate withdrawal without chronic opiate substitution therapy.<sup>66</sup> MAT with opiate substitution therapy is the most effective treatment for opioid dependence (OD).<sup>67,68</sup> Currently, several MAT options exist: methadone, buprenorphine, and naltrexone and are described in further detail in Table 89.2. Methadone and buprenorphine are the most effective MATs for treating

OD,<sup>69</sup> though naltrexone has achieved some success in highly motivated patients.<sup>70</sup> This is particularly true using the extended-release formulations.<sup>71</sup>

### MATs for Alcohol Use Disorders

Though pharmacotherapy for treating AUDs has been found to be superior to behavioral interventions, its use in PLWHAs has not been systematically evaluated.<sup>58,63,70,72–76</sup> There are currently three FDA-approved medications for managing AUDs: naltrexone, acamprosate, and disulfiram which are described further in Table 89.2. Naltrexone is the most effective treatment thus far for relapse prevention and treatment of AUDs.<sup>70,72</sup>



MAT, when appropriately dosed, is particularly important for HIDUs because it enhances access and adherence to ART and HIV treatment, improves retention in HIV care and decreases HIV risk-taking behaviors. As the number of HIDUs enrolled in MAT expand, so too must the knowledge of drug interactions that occur among MAT, ART and other medications to treat co-morbid conditions.<sup>60,77</sup> Details on these important pharmacologic interactions have been described previously.<sup>2,77</sup>

## Overview of Co-morbid Medical Conditions

Although the natural history of HIV disease among drug users is similar to that in other transmission risk categories, drug users are at increased risk for a number of other infections, including tuberculosis, bacterial pneumonia, skin and soft tissue infections, and endovascular complications.<sup>78</sup> Multiple features of injection drug use contribute to the increased risk of infection in this population.

These include:

- (i) Unsterile injection techniques
- (ii) Contamination of injection equipment or drugs with microorganisms, which may be present in residual blood in shared injection equipment
- (iii) Increased rates of skin, mucous membrane, and nasopharyngeal carriage of pathogenic organisms (including resistant organisms like methicillin-resistant *Staphylococcus aureus*)
- (iv) Poor dental hygiene
- (v) Impairment of gag and cough reflexes resulting in increased risk for aspiration and pneumonia
- (vi) Humoral and cell-mediated immunity deficits and phagocyte-mobility and killing defects induced by HIV infection and/or drug use
- (vii) Increased prevalence of exposure to certain pathogens (notably *Mycobacterium tuberculosis*)
- (viii) Alteration of the normal microbial flora by self-administered antibiotic use
- (ix) Concomitant behaviors such as cigarette smoking, alcohol use, or exchange of sex for drugs or money that increase risk of associated infections
- (x) Decreased access to and/or lack of appropriate use of preventive and primary healthcare services.

Recognition of co-morbid infections in HIDUs is critical to preventing significant medical complications and death but may be challenging because infections may present atypically in the setting of HIV-associated immunosuppression. Although most of these infections and other complications were common among drug users prior to the HIV epidemic, HIV has accentuated their incidence, severity, and clinical presentation.<sup>79,80</sup> In both inpatient and outpatient settings, these infections are often more common than specific HIV-related complications and often confound both diagnosis and treatment.<sup>35</sup> Table 89.3 summarizes the various infectious complications found in HIDUs by organ system.

**Table 89.3:** A Summary of Complications Related to Drug Use Among HIV-infected Injection Drug Users (Adapted from Bruce 2007)<sup>35</sup>

Location	Disease	Organism(s) or etiology	Treatment	Comments
Skin and soft tissue	Cellulitis	Group A and other streptococci, <i>Staphylococcus aureus</i>	Anti-staphylococcal and anti-streptococcal agents	Consider hospitalization; Consider MRSA depending on local epidemiology
	Abscess	Same as for cellulitis	Same as for cellulitis	Incision and drainage
	Necrotizing fasciitis	Polymicrobial, clostridial infections	Parenteral antibiotics to cover both Gram (+) and (-) organisms	Consider if crepitus noted; immediate surgical consultation required
	Septic thrombophlebitis	<i>Staphylococcus aureus</i>	Anti-staphylococcal agents	Surgical exploration and vein ligation
Cardio-vascular	Endocarditis	<i>Staphylococcus aureus</i> , streptococci, enteric Gram (-) rods	Anti-staphylococcal agents until cultures grow; Treat for 4–6 weeks;	Consider diagnosis of endocarditis if: (a) Regurgitant murmur; (b) Presence of peripheral or pulmonary emboli; (c) Blood culture (+); (d) Evidence of vegetation on echocardiogram
	Myocardial infarction (MI)	Substance induced – associated with vascular spasm and cocaine and AGS use; ↑d pro-inflammatory response from HIV and HCV; potential small ↑s from PI-based regimens	Fibrinolytics and supportive care; lipid-lowering agents among those with hyperlipidemia and smoking cessation	Drug-induced MI associated with no evidence of endovascular stenosis on angiography
Pulmonary	Community-acquired pneumonia	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , atypical organisms	PCN, cephalosporin, macrolide or tetracyclines	Treatment is typically empiric, based upon local epidemiology
		<i>Pneumocystis jiroveci</i>	TMP/SMZ, TMP/dapsone, atovaquone, pentamidine, primaquine/clindamycin	Most common when CD4 < 200 or CD4% < 14%; Consider even with normal chest X-ray

Location	Disease	Organism(s) or etiology	Treatment	Comments
		<i>Mycobacterium tuberculosis</i>	Isoniazid Rifampin Pryzinamide Ethambutol	Consider rifabutin due to PI interactions; Rifampin markedly decreases methadone and buprenorphine levels; start ART as soon as possible
		Atypical mycobacteria ( <i>M. kansasii</i> , <i>M. fortuitum</i> , <i>M. xenopi</i> , etc.)	Antimicrobials dependent on specific organism	
		Influenza A	Oseltamivir, zanamivir, amantadine, rimantadine	Influenza symptoms prolonged and influenza-related complications higher in HIV +; Influenza vaccination recommended annually
		H1N1	Oseltamivir, zanamivir	ART and increased CD4 associated with decreased hospitalization and mortality; H1N1 influenza vaccination recommended
	Septic emboli	<i>Staphylococcus aureus</i> , streptococci, enteric gram (-) rods	Anti-staphylococcal agents until cultures grow	Common complication in HIDUs, consider with pleuritic chest pain; treatment similar to endocarditis
Liver	Hepatitis	Hepatitis B virus	ART should be used in all co-infected patients and should include tenofovir + lamivudine or emtricitabine; Interferon occasionally for certain HBV genotypes; Entecavir and telbivudine used only if on fully suppressive ART regimen	Defined as being HBsAg positive; if HBV is to be treated, ART regimen should be used. Exclude hepatitis delta superinfection in all HBsAg + subjects.
		Hepatitis C virus	Pegylated Interferon + weight-based Ribavirin	Defined as being HCV antibody positive with detectable RNA
Nervous system	Altered mental status	Substance-induced psychosis	Observation and removal of the inciting agent	Includes opioids, cocaine, AGS, phencyclidine, psilocybin, ketamine, MDMA, others
		Brain abscess and embolism	Same as for endocarditis	CNS imaging (CT or MRI) used to monitor response to therapy
		Toxoplasma encephalitis	TMP/sulfadiazine or TMP/clindamycin	85–95% have positive anti-toxoplasma antibody; presentation typically with focal findings (e.g., seizure, altered mental status, CVA, etc.); CNS imaging (CT or MRI) used to diagnose and monitor response to therapy
		Tuberculosis meningitis or encephalitis	Same as for TB except INH dose ↑d to 600 mg per day	ART may be started cautiously, but may need serial lumbar punctures to ↓ intracranial pressure associated with immune reconstitution
		Cryptococcal meningitis	Amphotericin B induction followed by fluconazole maintenance	ART should be initiated as soon as possible (see TB meningitis)
		Dementia	ART is recommended	May be exacerbated by chronic drug use; Must rule out all other causes; diagnosis of exclusion
		Head trauma	May cause neurocognitive impairment and/or seizures	
	Neuropathy	HIV and HCV	Treatment aimed primarily at HIV and HCV	
	Cerebrovascular accident (CVA)	Substance-induced (cocaine, AGS)	Supportive care	Associated with 70% likelihood of developing depression
		Hemorrhage due to septic emboli	Same as for endocarditis	
Renal	Heroin or HIV-associated nephropathy	Both present with nephrotic syndrome	Renal biopsy to establish diagnosis Electron microscopy distinguishes diagnosis; ART should be started immediately for HIV-associated nephropathy	Focal and segmental glomerular sclerosis (FSGS) with progression to renal failure in weeks to months
	Glomerulonephritis	HBV, HCV	Treat underlying viral infection	
		Systemic bacterial infection	Same as for endocarditis	

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Abbreviations: ART, antiretroviral therapy; TB, tuberculosis; TMP/SMZ, trimethoprim/sulfamethoxazole; AGS, amphetamine-group substances; ↓/↑s, decreases/increases; ↓/↑d, decreased/increased; HBV, hepatitis B; HCV, hepatitis C; PCN, penicillin; CNS, central nervous system.

## VIRAL HEPATITIS

Chronic Hepatitis B and C are the most prevalent viral infections among IDUs, particularly HIDUs. They share HIV transmission routes, thereby commonly resulting in co-infection. Chronic HCV infection is the most common co-morbidity among HIDUs, occurring in approximately 20% of all PLWHA and in 60–90% of HIDUs. Although HCV transmission is primarily parenteral,<sup>81</sup> increased HCV sexual transmission has been associated with sex with an IDU among women<sup>82</sup> and traumatic sex practices and concomitant ulcerative sexually transmitted infections (e.g., syphilis, HSV) in men who have sex with men.<sup>83</sup> Incidence of perinatal transmission of HCV increases if the mother is co-infected with HIV.<sup>81</sup>

HIV co-infection among HCV-infected persons accelerates progression to end-stage liver disease (ESLD) and increases risk of hepatocellular carcinoma. A meta-analysis of HCV/HIV co-infected patients suggests cirrhosis develops in approximately 21% patients after 20 years and approximately 49% patients after 30 years of HCV infection<sup>84</sup> and decompensated cirrhosis is a leading cause of hospitalization and death in this population.<sup>85</sup> Among HIDUs, mean age of initiation of injecting is 17 years and HCV transmission typically occurs within the first 2 years of injection<sup>86</sup>; consequently, ESLD-related morbidity and mortality has increased as HIDUs live longer.<sup>87</sup> Moreover, HCV co-infection contributes to development or acceleration of cardiovascular disease,<sup>88</sup> neurocognitive impairment,<sup>89</sup> insulin resistance,<sup>90</sup> and renal insufficiency,<sup>91</sup> emerging co-morbidities that complicate care among PLWHAs.

Factors contributing to accelerated fibrosis progression in HIV/HCV co-infected persons include low CD4 counts, detectable HIV-1 RNA levels, use of hepatotoxic medications, and frequent alcohol use. HIDUs, compared to other PLWHAs, are more likely to present with advanced HIV disease and drink alcohol, thereby accelerating progression to ESLD.<sup>92</sup> Effective provision of ART, despite its potential for medication-associated hepatotoxicity, reduces HCV progression to ESLD.<sup>93</sup> It is recommended that HIV treatment be optimized prior to initiation of HCV treatment.<sup>94,95</sup>

Few HIDUs receive treatment for HCV. Reasons cited include cost, physician reluctance, unsubstantiated concerns about poor treatment adherence, misperception that HCV infection is not harmful, and pessimism about HCV treatment tolerability and efficacy among HIDUs.<sup>96</sup> There is admittedly much less published information about HCV treatment response in HIV/HCV co-infected patients but existing studies suggest a lower likelihood of their achieving a sustained virologic response to HCV treatment.<sup>94</sup> Despite these concerns, a growing number of studies in methadone clinics,<sup>97</sup> primary care settings,<sup>98</sup> and prisons<sup>99</sup> provide support for treating HIDUs for both HIV and HCV. Current therapeutic options for treating co-infected patients, including drug-drug interactions and the management of ESLD with transplantation, remain a challenge. Interested readers should consult more specialized texts.<sup>2,85,99–104</sup>

Chronic hepatitis B affects 10% of HIV-infected individuals worldwide, ranging from 5% in Western countries to 20% in some Asian and African regions where HBV is endemic.<sup>105</sup> In areas of low HBV endemicity, the virus is mostly transmitted through IDU and sexual contact, whereas in highly prevalent regions, HBV is mostly acquired through perinatal transmission.<sup>81</sup> Multiple concurrent hepatic viral infections complicate care among a subset of 3–5% of PLWHA, contributing greatly to poor outcomes.<sup>81</sup> HIDUs who do not have evidence of previous exposure to Hepatitis B should be vaccinated against the disease and counseled about safe injection practices to avoid exposure. All HIDUs requiring HBV treatment should be simultaneously treated with suppressive ART regimens. These regimens should minimally include two antivirals that effectively treat both infections.<sup>81,102</sup>

## TUBERCULOSIS

Tuberculosis (TB) and HIV have been tightly linked since the early years of the HIV/AIDS epidemic. TB has emerged as a leading cause of morbidity and mortality among HIDUs, especially in resource-poor settings. TB incidence has fallen or stabilized among IDUs in many industrialized countries but not in Eastern Europe and countries of the former Soviet Union.<sup>106</sup> Moreover, in many of the most populous countries of Asia, IDU contributes greatly to expanding HIV epidemics and high rates of TB. This awareness has unveiled the daunting challenges (see Box 89.1) confronting successful treatment of TB, HIV/AIDS, and SUDs.<sup>107</sup> The root cause of these epidemiological trends is multifactorial and related to the special challenges in diagnosing and managing both latent and active TB in HIDUs.

### Box 89.1 Critical Issues for Drug Users with TB and HIV Co-infection

- Intensive case finding and enhanced screening for identification of TB and HIV cases early in the course of disease
- Screening for latent tuberculosis infection (LTBI) and provision of isoniazid prophylaxis therapy (IPT)
- Enhanced airborne infection control in clinical care and other congregate settings (e.g., prisons, detention centers, drug treatment programs)
- Screening of all TB patients for HIV
- Screening of all HIV patients for TB
- Training and experience with special TB diagnostic challenges in HIV co-infected patients
- Recognition of the need for and implementation of adequate adherence support, including the use of directly observed therapy and linkage to supervised medication-assisted therapy (e.g., methadone or buprenorphine maintenance)
- Awareness of increasing rates of drug-resistant tuberculosis
- Appreciation of pharmacokinetic drug interactions among therapies to effectively treat substance abuse, HIV and tuberculosis
- Promoting and developing comprehensive, collaborative and integrated services for substance use, TB and HIV prevention and treatment services

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TB co-infection among HIDUs presents special diagnostic dilemmas. HIV-induced immunosuppression confounds diagnosis of latent TB, reducing tuberculin skin testing (TST) and newer interferon-gamma release assay utility; both are increasingly insensitive as immunosuppression progresses. Advanced HIV co-infection also confounds pulmonary TB diagnosis because of negative sputum smears (40–60% of infections), atypical chest radiographs, and high rates of difficult-to-diagnose extrapulmonary TB.<sup>108,109</sup> This is further exaggerated by poor access to care and advanced clinical presentation among HIDUs. When available, TB culture and drug-sensitivity testing requires weeks to months to complete. TB diagnosis among HIDUs is therefore delayed, often unconfirmed, influences treatment decisions and results in increased mortality.

Treatment of TB among HIDUs is also complicated. Contributing factors include additive toxicities, pharmacokinetic interactions, and special strategies needed for assuring treatment success. HIDUs experience increased frequencies of side effects and toxicities from TB and ARTs, likely resulting from the high prevalence of hepatic, renal, neurological, psychiatric, gastrointestinal, and hematologic co-morbidities among IDUs.<sup>35</sup> In terms of pharmacologic interactions, rifampin's effect on selected MAT and antiretroviral agents is particularly problematic.

TB treatment outcomes among HIDUs are less favorable than among other populations, not only because of these drug interactions but also because of structural and behavioral barriers to care. Treatment of SUDs is often prerequisite for successful HIV and TB treatment but lack of access to MAT is common where these co-morbid conditions occur. Stigmatization of HIDUs co-infected with TB further discourages this vulnerable population from accessing care in a timely fashion. Resultant poor adherence to therapy, decreased retention in care, and poor continuity of care between the community and prison setting frequently occurs, with increasing risk for TB and HIV drug resistance. This, in turn, reduces treatment success for both diseases in individual patients and increases transmission of resistant organisms to others. For this reason, the WHO advocates intensified TB case-finding among IDUs in non-medical settings. In addition to MAT, once in treatment, adherence support, directly observed therapy (DOT), and integrated healthcare delivery is strongly recommended and necessary to ensure long-term adherence and reduced morbidity and mortality.<sup>107,110</sup>

TB-associated morbidity and mortality among HIDUs results both from latent TB infection (LTBI), with increasing reactivation from HIV-induced immunosuppression, and from increased transmission in crowded and poorly ventilated settings where HIDUs congregate (e.g., prisons, drug treatment programs, and healthcare facilities). Latent TB reactivation among HIDUs is 9% *annually*, in contrast to a similar *lifelong* risk among HIV-uninfected populations with LTBI. Isoniazid preventive treatment (IPT) of LTBI has been demonstrated to be effective in HIDUs.<sup>111</sup> IPT, however, is prolonged and is associated with increased hepatotoxicity in the setting of HCV infection<sup>112</sup> and poor adherence, both major concerns among HIDUs. ART

also dramatically reduces TB incidence and recurrence among susceptible populations.<sup>113</sup> Prolonged use of IPT (36 months), coupled with ART in non-drug using PLWHA is associated with greater than 90% reduction in incident TB cases in TST+ individuals; however, IPT is less beneficial in TST- patients, and may be detrimental.<sup>114</sup>

On the other hand, treatment of drug-susceptible active pulmonary TB among HIDUs can be highly successful. Standard first-line TB treatment for HIDUs is the same as for others. Early diagnosis, adherence to combination anti-TB agents, and co-administration of ART are necessary components of successful treatment programs. Multiple observational studies demonstrate that ART reduces TB transmission and mortality from HIV/TB co-infection. A randomized clinical trial of integrated versus sequential TB and antiretroviral treatment demonstrated a 56% reduction in all-cause mortality in the integrated arm supporting both early ART initiation and integration of HIV and TB care.<sup>115</sup> Current WHO guidelines recommend initiation of ART among all PLWHA with TB, irrespective of CD4 count, as soon as possible within the initial phase of TB treatment.<sup>116</sup> Coordination and integration of services is crucial to ensure therapeutic success for HIDUs.<sup>110</sup>

Although most TB cases worldwide are susceptible to anti-TB therapy, drug-resistant TB has now emerged as a growing threat.<sup>117</sup> This problem is complicated among HIDUs by decreased TB treatment completion rates, resulting in selection of drug-resistant mutants and increased exposure to congregate settings that facilitate their transmission. Enhanced airborne infection control in congregate settings has been shown to prevent drug-susceptible and drug-resistant TB transmission to HIDUs.<sup>118</sup> Despite confirmed effectiveness of these strategies, their widespread application for HIDUs who frequent congregate settings remains limited.<sup>119</sup> Increasing numbers of cases of extremely drug resistant tuberculosis (XDR-TB) (MDR-TB plus resistance to second-line TB medications) worldwide have renewed global awareness of drug-resistant TB and its individual and public health impact.<sup>117</sup> As compared to drug-susceptible TB, treatment of drug-resistant TB is more complicated because available agents have less potency, increased toxicities, longer treatment duration, greater cost, and limited availability.

## OTHER INFECTIOUS COMPLICATIONS

Bacterial infections account for substantial morbidity and mortality among HIDUs, accounting for up to 25% of deaths.<sup>120</sup> These infections are commonly associated with syringe reuse, non-sterilization of the injection site, and injecting with crack or into sites other than the arm.<sup>121</sup> Injection breaches the natural integument defenses, increasing risk for both vascular and soft tissue injuries by exposing them to pathogens that may cause localized or systemic infections. Commensal staphylococcal and streptococcal species are predominantly involved. High *Staphylococcus* colonization rates among HIDUs, including methicillin-resistant strains of *Staphylococcus aureus*, contribute to

the high prevalence of bacterial infections in IDUs.<sup>122</sup> Methicillin-resistant strains of *Staphylococcus aureus* bacteremia has increased significantly in HIV-infected patients, and is associated with IDU, end-stage renal disease, and low CD4 counts.<sup>123</sup> Poor hygiene, injection of unsterile preparations, and unsterile injecting technique also predispose to infections with other bacterial pathogens such as *Pseudomonas*, clostridial, and candida species.<sup>124</sup>

Unusual bacterial infections and complications may result from contaminated drug or drug solutions. Some drug users crush tablets of prescription drugs, then dissolve and inject them intravenously or subcutaneously, resulting in infusion of filler agents commonly present in tablets including cornstarch, cellulose, or talc. These adulterants can become trapped by the pulmonary capillary bed and result in chronic inflammation and foreign body granulomatosis (e.g., talc lung).<sup>125</sup> These adulterants can also damage the endothelium of heart valves, resulting in increased risk of endocarditis.<sup>126</sup> Heroin and cocaine are often “cut” with various adulterants to enhance mind-altering properties or to substitute for pure drug (e.g., amphetamines, Ritalin, clenbuterol, dextromethorphan, fentanyl, ketamine, lidocaine, LSD [lysergic acid diethylamide], pseudoephedrine, quinine, scopolamine, or xylazine). Fatal outbreaks of wound botulism and other clostridial species, *Bacillus cereus* panophthalmitis, tetanus and aspergillus fungal infections caused by injection of contaminated heroin have been reported.<sup>127–129</sup>

Concomitant drug use portends additional complications to many organ systems, resulting in increased morbidity and mortality and complicating treatment (see Table 89.3). Bacterial infections range from the more prevalent localized skin and soft tissue infections (SSTIs) to less common deep-seated infections including pyomyositis, septic arthritis, osteomyelitis, and endocarditis.<sup>130</sup> IDUs who develop endocarditis are more likely to have tricuspid valve involvement but aortic or mitral valve involvement and HIV infection are associated with increased hospitalization,<sup>131</sup> morbidity, and mortality.<sup>132</sup> Clonal invasive Group A streptococcal infection outbreaks reported in Europe resulted in life-threatening infections among IDUs.<sup>133</sup> A Spanish surveillance study associated these outbreaks with specific environmental (drug-purchase site/dealer, homelessness) and injection-related (injection frequency, sharing paraphernalia) factors.<sup>134</sup> The cost of treating and managing injection-related SSTIs and their complications is considerable.<sup>135</sup> IDUs in the U.S. who sought care for SSTIs have increased risk for subsequent hospitalization and death. Visits for SSTIs therefore represent missed opportunities for preventive care for IDUs.<sup>136</sup>

### NON-INFECTIOUS END ORGAN COMPLICATIONS

Chronic kidney disease is increased among HIDUs and caused by infectious (e.g., HBV, HCV) and non-infectious etiologies, including direct medication-associated kidney damage<sup>137</sup> and, less commonly, heroin-related nephropathy.<sup>138</sup> Predisposing risk factors for chronic kidney disease, including African American race, low socioeconomic status, diabetes, and hypertension are highly prevalent

among HIDUs. Furthermore, proteinuria is more common among HIDU than uninfected IDUs and is associated with progression to end stage renal disease and cardiovascular morbidity.<sup>139</sup>

Cocaine and AGS increase blood pressure and vascular spasm of the coronary and cerebral arteries, resulting in myocardial infarction and cerebrovascular accidents. Atherosclerosis that results in increased cardiovascular disease is reduced by ART, but is accelerated by chronic inflammation from HIV and HCV infections and by some protease inhibitors.<sup>88</sup>

Non-AIDS malignancies are emerging as ART successfully averts development of opportunistic infections. Infection-related cancers (anal and liver cancer, Hodgkin lymphoma) and non-infection-related cancers (e.g., of lung, skin, non-Hodgkin lymphoma) are increasingly reported.<sup>140</sup> European and North American cohort studies, where ART is readily available, remind us that non-AIDS complications are emerging as leading causes of mortality among PLWHAs.<sup>141</sup> Absent from these cohorts is a concentration of HIDUs but these non-AIDS co-morbidities are already straining healthcare delivery issues and are likely to grow with time in regions where injection drug use is rising.

### MENTAL ILLNESS

A thorough discussion of mental illness as it relates to substance misuse and HIV is beyond the scope of this chapter. It should be noted, however, that mental illness among HIDUs is associated with high-risk behaviors,<sup>142</sup> decreased adherence to ART, and HIV clinical progression.<sup>143,144</sup>

## Issues in Special Populations

### WOMEN

Women who inject drugs experience extraordinary stigma and sometimes cultural condemnation. They may face discrimination both because of their drug use and of their gender.<sup>12</sup> Published research to date on female IDUs centers on the concept that women's drug use is driven by and embedded within social relationships. In this social context, specific patterns of injection drug use among women pose exquisitely high risk for acquisition of HIV. Women are more likely than men, for example, to begin injecting at a younger age, to be introduced to injecting by either male sexual partners or other female friends, and to have used other illicit drugs for less time before first injecting.<sup>145–147</sup> Because female IDUs often depend on others to acquire drugs and because they use drugs in dyads, they are more likely to be injected by someone else and to have ever shared needles or other drug paraphernalia.<sup>146–149</sup> As such, women are often “second on the needle” and therefore experience increased risk of exposure to HIV and viral hepatitis.<sup>146,148</sup> This dependency on others to obtain, prepare, and inject drugs perpetuates a power imbalance within relationships in which women have limited autonomy in modifying their drug-use behaviors.<sup>12</sup> They may also be forced to rely on sexual bartering for drugs, further potentiating HIV risk. In this role, women are also subject to increased risk of sexual

and physical intimate partner violence, the prevalence of which is three times higher in drug-involved women than in women who do not use drugs.<sup>150,151</sup> Among female IDUs, violence is considered an independent risk factor for HIV exposure and acquisition.

Drug-dependent women are doubly at risk for HIV because of overlapping sexual and drug networks. While some drug-involved women inject with their sexual partners, others do not inject drugs but have high-risk sexual partners who do. In New York City, for example, recent surveillance data revealed that 8% of heterosexual HIV diagnoses in 2001–2007 were attributed to sex partnerships between male IDU and female non-IDUs.<sup>152</sup> A pooled estimate of the risk of HIV transmission between infected IDUs and their sexual partners was 1 in 2000–5000 heterosexual sex acts.<sup>153,154</sup> These heterosexual IDU sex partnerships were associated with unprotected sex, heavy crack use, incarceration, and poverty, each of which independently contribute to HIV risk.<sup>152</sup>

Treatment of HIV-infected women follows standard guidelines, except during pregnancy in which teratogenic antiretrovirals and single-dose regimens should be avoided.<sup>155,156</sup> A complete discussion of the treatment of HIV in pregnancy and mother-to-child transmission of HIV is beyond the scope of this chapter but is discussed elsewhere in this book. Treatment of SUDs in HIV-infected women is similar to that of their male counterparts but data are sparse on MAT during pregnancy, in part because the topic of drug use in pregnancy is highly stigmatized.<sup>12,147,148,157,158</sup>

## INCARCERATED HIV-INFECTED DRUG USERS

The high rates of HIV among prisoners globally is directly associated with society's approach to controlling illicit drug use. Mass incarceration of drug users has resulted in concentration of HIV/AIDS, TB, and other co-morbidities within prisons compared to surrounding communities.<sup>165</sup> While the single most important strategy in controlling HIV in prison is to stem the rate of incarceration itself,<sup>159</sup> ample evidence suggests that the criminal justice system can be an effective place to identify and treat HIV and SUDs when appropriate services are available.<sup>160</sup>

Incarceration itself increases HIV risk, through a cascade of multiple factors, including disruption of social networks,<sup>161,162</sup> multiple partners and high-risk sexual behaviors that are associated with mass incarceration,<sup>163</sup> and reduced likelihood for gaining meaningful employment or entrance into social service and rehabilitation programs. Inadequate treatment of mental illness and lack of social support puts prisoners at a greater risk of relapsing SUDs and reincarceration.<sup>164</sup> Most incarcerated HIDUs have limited or no access to ART or MAT. When widescale ART is prescribed in prison settings, prison-related HIV mortality achieves parity with the community.<sup>165</sup> Highly structured prison or jail settings may also provide opportunities to initiate treatment for SUDs. Despite a large body of evidence, very few MAT programs transitioning HIDUs from prison to the community have been developed.<sup>166</sup> Treatment benefits may therefore be lost beyond the period of incarceration.<sup>167–169</sup>

## Overcoming Healthcare Disparities in HIV-Infected Drug Users

The life of a drug-dependent patient is often chaotically organized around substance use needs. Access to drugs may replace even the most basic human needs, including food, clothing, shelter, safety, and healthcare. To engage HIDUs in care, health providers should offer integrated medical, psychiatric, and social services in a convenient way. Successful programs for this population have developed some or all of the following characteristics:

- (i) Pharmacologic (e.g., methadone or buprenorphine treatment program)<sup>170</sup> and/or non-pharmacological treatment (e.g., behavioral interventions) for substance use<sup>170,171</sup>
- (ii) Flexible outpatient and community care settings (e.g., walk-in clinics, mobile healthcare programs)<sup>172</sup>
- (iii) Low-threshold sites to engage active users (e.g., syringe exchange sites)<sup>173</sup>
- (iv) Directly administered ART<sup>174,175</sup>
- (v) Intensive outreach and case management services<sup>176,177</sup>
- (vi) Treatment during incarceration<sup>168,178</sup>

## HIV Prevention and Risk Reduction Strategies

The relapsing pattern of drug use and the wide array of associated severe medical consequences require the development of preventive risk reduction strategies. Risk reduction does not promote injection drug use, but seeks to decrease the frequency of adverse events that are related to this practice, including HIV transmission. Risk reduction is based on the underlying principle that injection drug use is a chronic and relapsing disease that may not be cured in the individual or eliminated from society but can be conducted in a way that minimizes harm to the user and others. While complete cessation of drug use remains a laudable goal, reduction in drug use frequency and safer injection practices are more realistic goals for many drug users until abstinence can be achieved. Risk reduction strategies have been effectively incorporated into some drug treatment programs, syringe exchange programs, and safe injection rooms.<sup>179–181</sup>

There are two main types of interventions to decrease injection-related HIV transmission: (i) those that seek to reduce the total number of injections (i.e., quantity) and (ii) those that aim to reduce unsafe injection practices (i.e., quality).<sup>154</sup> Programs designed to reduce the total number of injections include treatment for SUDs and criminal punishment for SUDs. Effective drug treatment, primarily through MAT, is a very effective way to reduce drug-related harm but these therapies do not reach many IDUs. In 126 reporting countries, only 8 per 100,000 IDUs were receiving opioid substitution therapy.<sup>182</sup> Furthermore, even with marked risk reduction in this setting, opioid-dependent drug users may continue to inject, primarily with non-opioids. As such, there is a need for further risk reduction using other methodologies. There is less consistent published data on the reduction of injections with behaviorally based drug treatment interventions. Where MAT coverage is insufficient, it is imperative to have available access to clean needles and syringes.



Needle and syringe exchange programs are critical primary and secondary prevention interventions for IDUs, particularly those who are HIV-infected.

In some countries, primarily in Southeast Asia, efforts to reduce injection-related HIV transmission by dissuading drug use have devolved into criminalization of drug use. As part of extra-judicial systems, drug misusers are detained in closed settings and receive little treatment for SUDs or education about HIV prevention. As such, these systems are ineffective at either curbing HIV transmission within these drug detention centers or preventing relapse to drug use upon release.<sup>154</sup>

Other programs seek to secondarily prevent HIV by reducing unsafe injection practices. Education about hygienic injection practices and the provision of drug use paraphernalia are essential to HIV prevention services. These programs have been shown to be cost-effective in settings with high HIV prevalence.<sup>154</sup> Still, only 8% of IDUs worldwide access needle and syringe exchange programs on an annual basis.<sup>182</sup> In addition to the distribution or exchange of injection equipment, these programs typically include HIV/AIDS education, condom distribution, and referral or enrollment in a variety of drug treatment, medical, and social services.<sup>183</sup> Specifically, some programs provide onsite medical and drug treatment, resulting in reductions in emergency department use by IDUs.<sup>173</sup> Provision of primary medical care services linked to drug-abuse treatment is a way to promote preventive therapies to enhance harm reduction. In this and all other clinical settings, in addition to the treatment of HIV disease and prevention of complications, injection drug users should be routinely screened for Hepatitis B and C, latent *Mycobacterium tuberculosis* infection, syphilis, and other sexually transmitted diseases. They should be offered pneumococcal, influenza, tetanus, and hepatitis B immunization and (when appropriate) prophylaxis for TB.<sup>184</sup>

Effective strategies for secondary HIV prevention in HIDUs should include sexual risk reduction in addition to drug-related risk reduction.<sup>185</sup> This is especially important for female partners of IDUs, for whom sex constitutes the major risk behavior for HIV acquisition. Although better studied in non-IDU populations, sexual risk reduction for serodiscordant couples includes education about and provision of condoms, testing and treating high-risk cohorts for HIV, and reduction of HIV viral load with ART to reduce infectivity.<sup>154</sup> There is limited information available on the provision of ART to HIDUs but, of 47 countries who recently reported, only 4 HIDUs were receiving ART for every 100 in the population.<sup>182</sup> This suggests a need for antiretroviral scale-up to treat HIV among IDUs and decrease HIV transmission among serodiscordant couples.

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## Summary

- The drugs most commonly associated with HIV infection worldwide are heroin, cocaine, and amphetamine group substances but both injection and non-injection drug use are associated with increased HIV-related risk-taking.
- HIDUs face numerous social and structural barriers to care, such that any potential benefits of HAART on HIV-related morbidity and mortality are lost because HAART is either not offered or because drug users receive discontinuous care. Furthermore, HIDUs are often labeled as “difficult patients” because HIDUs experience multiple co-morbidities, especially HCV, TB, skin and soft tissue infections, and mental illness.
- Effective strategies for overcoming healthcare disparities for HIDUs include addressing HAART adherence and promoting secondary prevention of HIV. Ample evidence suggests that the criminal justice system (CJS) can be an effective place to identify and treat HIV when appropriate services are available.
- Treatment of substance use disorders is equally vital. Greatest evidentiary support is for methadone and buprenorphine as opiate substitution therapies. Providers should be aware, however, of pharmacological interactions between MAT therapies and HAART.
- Most importantly, to engage HIDUs in care, health providers should offer integrated medical, psychiatric, and social services in a convenient way.

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# section **xiii**

## **SEXUALLY TRANSMITTED INFECTIONS IN SPECIAL GROUPS OF POPULATIONS**

— *Mikhail Gomberg*

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All sexually transmitted infections (STIs) considered together represent one of the common infectious diseases both in developed and developing worlds. STIs are more prevalent in teenagers and young adults of reproductive age group. Of the various STIs, syphilis, gonorrhea, chlamydia, hepatitis B virus, HIV, HPV, and herpes simplex infections carry a potential impact on maternal, fetal, and neonatal health, while other STIs like *T. vaginalis* and bacterial vaginosis (BV) also contribute to adverse pregnancy outcome. With untreated STIs, post delivery infections are more in frequency and severity. Immunological changes occurring during pregnancy like decrease in CMI, Th1 type cytokines, and other proinflammatory cytokines make the woman more susceptible to infections in which Th1 response is important for protection against viral infections as well as infection with intracytoplasmic pathogens.<sup>1,2</sup> Developing targeted interventions to reduce STI related maternal and infant morbidity are critical public health issues. Pregnancy provides an opportunity for screening and treatment of these infections to minimize or eliminate antepartum, intrapartum, and postpartum consequences of most STIs.

### Syphilis in Pregnancy

Syphilis in pregnancy represents an important cause of fetal and neonatal loss in many developing countries. In parts of Africa, the prevalence of syphilis among antenatal clinics has been found to be as low as 1.1% in Nigeria and as high as 17.4% in Cameroon.<sup>3,4</sup> The continued high prevalence of syphilis at delivery has been associated with HIV infection, substance abuse, lack of prenatal care, and treatment failure.<sup>5</sup> However, the rates of syphilis in the US have declined since 1990 and it was a record low of 2.6 cases per 100,000 persons, likewise a record low incidence of congenital syphilis (CS), 20.6 per 100,000 live births in 1998,<sup>6</sup> which further declined to 13.4/100,000 live births in 2000.<sup>7</sup> However, the rate of CS in the US has started to creep back up after plummeting over the last two decades.<sup>1</sup> The incidence of CS has gone up from 8.2 cases per 100,000 live births in 2005 to 10.1 in 2008 with most of the increase having occurred in the

South. CS rates in infants born to black mothers have gone up from 26.6 in 2005 to 34.6 per 100,000 live births in 2008 and now account for half of all CS cases. Since CS is transmitted from mothers with syphilis, CS rates have historically tracked the combined primary and secondary syphilis rate seen in women, which has also started to climb.<sup>8</sup>

### CLINICAL MANIFESTATIONS

Syphilis is divided into various clinical stages—primary, secondary, tertiary, and latent. Latent infection is subdivided into early latent (<1 year duration) or late latent (>1 year duration).

Primary syphilis, which manifests with a painless chancre, follows an incubation period of 10–90 days but it is usually less than 6 weeks. During pregnancy the primary lesions may be of much smaller size or be so located as to go unnoticed. Cervical chancre is more common in pregnancy because of the easy inoculation of the friable cervix. Primary chancre is characterized by a painless, firm ulcer with raised edges and a base with cleaner granulation. It persists for 2–6 weeks and then heals spontaneously, and is often accompanied by nontender, unilateral enlarged and firm inguinal lymph nodes. Six to eight weeks after the primary chancre, secondary syphilis usually appears in the form of a highly variable skin rash. About 15% of the women may still have the remains of chancre when the rash of secondary syphilis appears. The lesions of secondary syphilis may go unnoticed in about one-quarter of the patients. Rash during secondary syphilis does not cause itching and is not bright enough to be noticed to inexperienced eye. In some, the lesions are limited to genitalia as elevated areas or condylomata lata, which occasionally cause vulval ulceration. The disease in an unsupervised pregnant mother may go unnoticed and delivery of a stillborn baby or live baby with severely infected CS may be the only suggestion of the disease in the mother. Recent Centers for Disease Control and Prevention (CDC) data show that 6.5% of US infants with CS in 2008 were stillborn or died within 30 days of birth.<sup>9</sup>

Syphilis in pregnancy may be associated with increased risk of fetal demise, intrauterine growth retardation, and preterm delivery.

However, most frequent and potentially ominous complication of syphilis is congenital infection with *T. pallidum*. Approximate frequency of occurrence of CS is 50% with untreated mother in primary and secondary stage of disease, 40% with early latent and 10% occurrence with late latent and tertiary syphilis.

Clinical manifestation of early CS can be maculopapular rash, snuffles, mucosal patches, hepatosplenomegaly, jaundice, pneumonia, lymphadenopathy, chorioretinitis, and iritis.

### DIAGNOSIS OF MATERNAL SYPHILIS

Non-treponemal Venereal Disease Research Laboratory and rapid plasma reagin tests are accepted as screening diagnostic tools at the first prenatal visit. Because these reagin tests lack specificity, a treponemal test such as fluorescent treponemal antibody absorption test (FTA-ABs) or microhemagglutination assay (TPHA) for detecting antibodies to *T. pallidum* are used to confirm a positive result, especially in women at high risk for syphilis. Enzyme linked immunosorbent assay (ELISA) for syphilis which had a sensitivity and specificity of 100% and 90%, respectively, in a study of 265 specimens has also been used in some centers.<sup>10</sup>

### PATHOPHYSIOLOGY OF CONGENITAL SYPHILIS

Syphilis is neither a new disease nor a newly recognized one. Some of the basic facts of congenital involvement such as Hutchinson triad<sup>11</sup> and Kassowitz's observation in 1846 that the longer a woman has syphilis before pregnancy occurs, the less likely it is that her fetus will die *in utero* or be born with CS<sup>12</sup> have been known for over 100 years.

Despite long history of medical interest in syphilis and its effect on pregnancy outcome, many fundamental questions about the pathophysiology and treatment of syphilis during pregnancy remain unanswered. However, understanding has been advanced by recent reports that delineate the complete sequence of the genome of the syphilis spirochete *Treponema pallidum*, which provide a more precise description of fetal and neonatal infection by use of rabbit infectivity tests, and describe the gestational age distribution of fetal death due to syphilis.<sup>13</sup>

Syphilis is readily transmitted from mother to baby. Spirochetes may easily cross the placenta which results in congenital infection. The probability of transmission of infection to fetus is nearly 100% if mother has early syphilis when there is spirochaetemia,<sup>14</sup> it is 70%, 4 years after acquisition of maternal syphilis.<sup>15</sup> Most infants born to mothers with late latent syphilis are uninfected. The theory that *T. pallidum* is not able to cross the placental barrier until 20 weeks of pregnancy no longer holds true.<sup>16</sup> Using silver stain and immunofluorescence technique, spirochaetes were identified in abortuses as early as after 9–10 weeks of gestation.<sup>17</sup> Using rabbit infectivity test alive *T. pallidum* were identified in amniotic fluid between 14–19 weeks period of gestation.

Hollier et al.<sup>18</sup> in a study on 24 pregnant women with maternal syphilis showed evidence of fetal infection in 16 cases.

Hepatomegaly, fetal ascites, enlarged placenta, and abnormal liver function test were observed in these fetuses. However, this work still fails to address the involvement of the central nervous system (CNS), a critical question that has influenced recommendations for treating CS. Michelow et al.<sup>19</sup> evaluated 140 infants born to mothers with syphilis and showed that 22% has positive result of the rabbit infectivity test on CSF. The evidence suggested that CSF involvement was more likely if maternal syphilis was categorized as secondary or early latent.

Syphilis affects the placenta which becomes large and pale. Microscopically, the villi appear to lose their characteristic arborescent appearance and become thicker and club-shaped. There is marked decrease in the number of blood vessels that in advanced cases almost disappear as a result of endarteritis and proliferation of stromal cells. Related to this, there is increased vascular resistance in the uterine and umbilical artery<sup>20</sup> contributing to intrauterine growth retardation and fetal death.

### SCREENING FOR SYPHILIS IN PREGNANCY

CDC,<sup>21</sup> American College of Obstetricians & Gynecologists (ACOG),<sup>22</sup> and US Preventive Services Task Force (USPSTF), 2009,<sup>23</sup> recommend that all pregnant women should be screened for syphilis during pregnancy at the first prenatal visit. High-risk women should have repeat screening in 3rd trimester. Women who had delivered a non-immune hydropic fetus or experienced a stillbirth or has the diagnosis of hydrops on ultra sound should also undergo screening for syphilis. Women not tested for syphilis during pregnancy should be tested for syphilis at the time of delivery/labor.

### TREATMENT

Centres for Disease Control and Prevention (CDC)<sup>21</sup> recommends treating early syphilis (primary, secondary, or early latent) with a single dose of 2.4 million units of benzathine penicillin G (7.2 million units over three weeks with 2.4 mu weekly for late latent syphilis or latent syphilis of unknown duration).

From retrospective studies it is observed that benzathine penicillin G cures early maternal syphilis and prevents neonatal syphilis in 98% of cases.<sup>24</sup> In UK, specialists favor prolonged parenteral course of procaine penicillin, and in the US, a single injection of benzathine penicillin G is recommended for the treatment of early infectious syphilis. However, the superiority of one regimen over the other has not been proved. CDC guidelines for the treatment of syphilis in pregnancy recommend the same dosage schedule of benzathine penicillin G as for non-pregnant adults. Some recommend a second dose of benzathine penicillin G, 2.4 million units IM one week after the initial dose, especially for women in the third trimester or for women with secondary syphilis during pregnancy. (For more treatment details refer to Chapter 36 on Infectious Syphilis.)

A review of the success of maternal treatment to prevent CS by stage of infection showed that treatment according to CDC recommendations was 100% effective in preventing CS in all the

27 cases of primary and 136 cases of late/latent syphilis and it was 94.7% effective in 71 of the 75 cases of secondary syphilis.<sup>25</sup>

Walkar et al.<sup>26</sup> in a Cochrane review in 2001 concluded that although there is no doubt that penicillin was effective in treating maternal syphilis and in preventing CS, there was uncertainty about the optimal treatment regimen.

Another study by Wendel et al. in 2002<sup>27</sup> concluded that the available evidence did not indicate that any regimen was more effective than 2.4 million units of benzathine penicillin G for treating early syphilis. Watson-Jones et al.<sup>28</sup> in a study on 1688 pregnant women reported that there was no increased risk of adverse pregnancy outcome in women treated with single dose of benzathine penicillin as compared with seronegative women. This was an important observation since other works had suggested that pregnant women with syphilis who received more than 2–3 doses of benzathine penicillin have better pregnancy outcome than women who receive only one dose.<sup>29,30</sup>

The treatment of syphilis in pregnancy can lead to Jarisch–Herxheimer reaction. In a study of 50 pregnant women who received treatment, 40% experienced Jarisch–Herxheimer reaction and 13 developed regular uterine contractions. Although all resolved without the precipitation of labor, 12 developed variable deceleration of fetal heart rate tracings.<sup>31</sup>

Other antibiotics are also effective against syphilis. Tetracyclines are effective, but are contraindicated in pregnancy because of the discoloration of fetal decidua teeth. Erythromycin is thought to be effective but crosses the placenta poorly, and there have been reports of CS occurring despite “adequate” therapy with erythromycin.<sup>32</sup>

The management of women allergic to penicillin is based on observational studies. Patients with a history of penicillin allergy can be skin tested to confirm the risk of an IgE mediated allergic reaction to penicillin. If skin tests are reactive, penicillin desensitization should be undertaken and then followed by penicillin treatment. The consequences for the fetus of mothers with failed desensitization are unclear. UK guidelines recommend erythromycin therapy and follow-up of the baby. Cephalosporins such as ceftriaxone and newer macrolide antibiotics like azithromycin may prove useful but have not been adequately evaluated.

## DIAGNOSIS AND TREATMENT OF CONGENITAL SYPHILIS

In resource-poor settings the diagnosis of CS is largely based on the use of Venereal Disease Research Laboratory or rapid plasma reagin serological tests.<sup>33</sup> However, these tests detect IgG, which may be passively transferred transplacentally from mother to fetus and interpretation of a positive test is difficult. A comparison of maternal titers with infant's titers may be helpful to some extent. A four-fold higher or rising titer in infant is considered as significant.

Immunoblot may be helpful in diagnosing CS. The value of tests like a lumbar puncture or bone radiograph in asymptomatic infants is doubtful, as the former has a low sensitivity in

asymptomatic infants and the radiological changes are found only in about 20% infants.<sup>33</sup>

In developed countries, guidelines recommend that treatment decision be based on:

- Identifying syphilis in the mother
- Confirming the adequacy of maternal treatment
- Identifying clinical, laboratory or radiographic evidence of syphilis in the infant;
- Comparing maternal non-treponemal serological titers (at delivery) with the infant's non-treponemal titres.<sup>33</sup>

Symptomatic infants or those with abnormal spinal fluid examination can be treated with aqueous penicillin G, 100,000–150,000 IU/kg/day given IV in two to three divided doses each day for at least 10 days, or procaine penicillin G 50,000 IU/kg IM daily for a minimum of 10 days. Asymptomatic seropositive infants with normal CSF can be treated with a single dose of benzathine benzylpenicillin 50,000 IU/kg administered IM. Infants born to mothers treated with erythromycin should be treated as if they have CS.

## Gonococcal Infection in Pregnancy

Next to genital chlamydial infections, gonococcal infection is the most frequently reported sexually transmitted disease in the US.<sup>34</sup> The prevalence of gonococcal infection during pregnancy varies but may be as high as 7% and reflects the risk status of the population.<sup>35,3</sup> Risk factors include being single, adolescent, poverty, drug abuse, prostitution, other STIs and, lack of prenatal care. Gonococcal infection is also a marker for concomitant chlamydial infection in about 40% of the infected pregnant women,<sup>36</sup> while overall prevalence of coinfection varies from 30 to 46%.<sup>37,38</sup>

In most pregnant women, gonococcal infection is limited to the lower genital tract, including the cervix, urethra, and periurethral, and vestibular glands. Acute salpingitis is rare but develops if the cervical infection ascends before the obliteration of the uterine cavity through the fusion of the chorion and decidua at 12 weeks. Pre-existing infection can cause a tubo-ovarian abscess, but this is even rarer.

Gonococcal infection in any trimester may have deleterious effects on the pregnancy outcome. There is an association between untreated gonococcal cervicitis and septic spontaneous abortion or infection after induced abortion.<sup>39</sup> Preterm delivery, prematurely ruptured membranes, chorioamnionitis, and postpartum infection are more common in women with *Neisseria gonorrhoeae* detected at delivery.<sup>40</sup> Attributable risk for preterm birth has been reported as 14%.<sup>41</sup> Expectant management of the culture-positive woman has been recommended even with prematurely ruptured membranes as long as antimicrobial treatment was given promptly.<sup>42</sup>

There is some evidence that pregnancy alters the clinical presentation of gonococcal infections. Increased rates of oropharyngeal and anal infections in pregnancy have been reported.<sup>43,44</sup> The increased incidence of non-cervical infection may be due to altered sexual practices because of pregnancy, cultural



customs or both. It is also interesting that pregnant women account for a disproportionate number (7–40%) of disseminated gonococcal infections<sup>44,45</sup> which is caused by hematogenous spread of *N. gonorrhoeae* from the primary site. Pregnancy, as well as menses and terminal component complement deficiencies may also increase the risk for disseminated gonococcal infection as a result of endometrial exposure of submucosal vessels to the infecting organisms.<sup>46,47</sup> Disseminated gonococcal infection typically manifests as arthritis, tenosynovitis and dermatitis but can also present as perihepatitis. Rarely endocarditis, meningitis and osteomyelitis occur. Skin lesions appear initially as small vesicles that subsequently become pustules and develop a hemorrhagic base.<sup>48</sup>

### GNOCOCCAL INFECTION AMONG NEONATES AND INFANTS

Gonococcal infection among infants usually results from exposure to infected cervical exudates at birth. It is usually an acute illness that manifests 2–5 days after birth. The prevalence of infection among infants depends on the prevalence of infection among pregnant women, whether pregnant women are screened for gonorrhea and whether newborns receive ophthalmia prophylaxis. The most severe manifestations of *N. gonorrhoeae* infection in newborn are ophthalmia neonatorum and sepsis, which can include arthritis and meningitis. Less severe manifestations include rhinitis, vaginitis, urethritis, and infection at sites of fetal monitoring. Identifying and treating this infection is especially important because ophthalmia neonatorum can result in perforation of the globe of the eye and blindness.

### DIAGNOSIS

Because of the lower sensitivity (as compared to symptomatic men) Gram stain of endocervical, pharyngeal or rectal specimens is not sufficient to detect infection and therefore is not recommended. Specific testing for *N. gonorrhoeae* is recommended because of the increased utility and availability of highly sensitive and specific testing methods and a specific diagnosis might enhance partner notification.

Specific diagnosis of infection with *N. gonorrhoeae* may be obtained by testing endocervical, vaginal or urine specimens. Culture, nucleic acid hybridization tests and NAAT are available for detection of genitourinary infection with *N. gonorrhoeae*.<sup>49</sup>

In all cases of neonatal conjunctivitis exudates should be cultured for *N. gonorrhoeae*. A definite diagnosis is important because of the public health and social consequences of a diagnosis of gonorrhea.

### TREATMENT

Pregnant women should not be treated with quinolones or tetracyclines. Those infected with *N. gonorrhoeae* should be treated with a recommended regimen like ceftriaxone 125 mg, or 250 mg IM in a single dose or cefixime 400 mg orally in a single dose. Women who cannot tolerate a cephalosporin should be administered a single 2 g dose of spectinomycin IM. Either

azithromycin or amoxicillin are recommended for a treatment of presumptive or diagnosed co-infection with *C. trachomatis* infection during pregnancy.

Though single-dose treatment is sufficient for uncomplicated infection, treatment should last not less than 7 days for disseminated gonococcal infection. For gonococcal endocarditis, therapy should be continued for at least 4 weeks and for meningitis for 10 to 14 days. Endocarditis rarely complicates pregnancy and it may be fatal.<sup>50</sup>

Recommended regimen for gonococcal conjunctivitis is ceftriaxone 25–50 mg/kg IV or IM in a single dose, not to exceed 125 mg. Topical antibiotic therapy alone is inadequate and is unnecessary if systemic treatment is administered.

It is also recommended that the mother and infant be evaluated for concomitant chlamydial infection. Isolation is recommended until treatment for 24 hours. Both parents should also be investigated appropriately and treated.

### Bacterial Vaginosis

Bacterial vaginosis (BV) is defined as replacement of normal, healthy vaginal lactobacilli by a characteristic set of genital anaerobes, mycoplasmas, and *Gardnerella vaginalis*. BV has been detected among 10–41% of women in various studies.<sup>51–54</sup> Women seen in sexually transmitted disease clinics have the highest prevalence of BV, up to 64%.<sup>55,56</sup> Studies in pregnant women demonstrate prevalence for BV similar to those found among the non-pregnant populations.<sup>57–59</sup> 50% of cases with BV resolve spontaneously during pregnancy.<sup>60–61</sup> Symptoms include vaginal discharge, pruritus, or malodor although half of the women are asymptomatic.<sup>62–64</sup>

### OBSTETRICAL COMPLICATIONS

Considerable information from around the world links BV directly to a number of serious obstetrical complications, including spontaneous abortion, preterm birth, preterm labor, preterm premature rupture of membranes (PROM), amniotic fluid infection, postpartum endometritis, and postcaesarean wound infections. Risk ratios (RR) range between 1.1 and 7.3 in these studies and have been overwhelmingly significant.<sup>65–67</sup> Most importantly, BV represents a potentially preventable risk factor for these common and costly complications of pregnancy.

### DIAGNOSIS

BV can be diagnosed by the use of clinical or Gram stain criteria. Clinical criteria require three of the following symptoms or signs:

- A homogeneous, white, non-inflammatory discharge that smoothly coats the vaginal walls
- The presence of clue cells on microscopic examination
- pH of vaginal fluid greater than 4.5
- Fishy odor of vaginal discharge before or after the addition of 10% KOH (the whiff test).

A Gram stain is used to determine the relative concentration of the bacterial morphotypes characteristic of the altered flora of

BV, which is an acceptable laboratory method for diagnosing BV. Culture of *G. vaginalis* is not recommended because it is not specific. However, quantitative measurements of *G. vaginalis* using specific DNA probes can serve as a useful aid in diagnosing BV.<sup>68</sup> Cervical Pap tests have limited clinical utility for the diagnosis of BV because of low sensitivity. Other commercially available tests that may be useful for the diagnosis of BV include a card test for the detection of elevated pH and trimethylamine which is produced by anaerobic bacteria and *Mobiluncus* spp.

## SCREENING

The recent awareness of the possible adverse sequelae of BV infection has led to more attention to the screening and treating of women for this condition during pregnancy. An economic model linking perinatal conditions to BV from evidence in the literature to resultant hospital charges concluded that the direct costs of preterm labor, preterm delivery, low birth weight, and other complications associated with BV totaled nearly \$1.0 billion.<sup>67</sup> However, asymptomatic women or women without risk factors do not need routine screening and treatment.<sup>69,70</sup>

## TREATMENT

All pregnant women who have symptomatic disease require treatment. Some specialists prefer using systemic therapy to treat possible subclinical upper genital tract infection. Treatment of BV in asymptomatic women at high risk for preterm delivery has reduced incidence of preterm delivery in three of four randomized controlled trials.<sup>71–74</sup> Recommended treatment is metronidazole 500 mg orally twice a day for 7 days or metronidazole orally 250 mg three times a day for 7 days or clindamycin 300 mg orally twice a day for 7 days. However, concerns have been raised that metronidazole treatment may increase preterm birth in certain populations (often at high doses) up to two times.<sup>75,76</sup>

The treatment of the male partner remains controversial.<sup>77</sup> General clinical trials indicate that a woman's response to therapy and the likelihood of relapse or recurrence are not affected by the treatment of her sex partner(s).

## Trichomonas Infection

Trichomoniasis is caused by the protozoan *T. vaginalis*. Many infected women have symptoms characterized by diffuse, malodorous, yellow green vaginal discharge with vulvar irritation. However, some women have minimal or no symptoms on vaginal examination, in many others vaginal mucosa is erythematous and punctate hemorrhages may be present on the cervix (strawberry cervix).

## DIAGNOSIS

*T. vaginalis* are found readily in a wet mount of vaginal secretion as flagellated, ovoid, motile organisms. The sensitivity of this method is generally considered to be about 85%. *Trichomonas*

are identified most accurately by culture using Diamond medium; however, DeMeo et al. have shown that a DNA probe test was 90% sensitive and 99.2% specific.<sup>78</sup>

Other FDA cleared tests for trichomoniasis in women include OSOM *Trichomonas* Rapid Test and Affirm TMVP III test. The results of OSOM *Trichomonas* tests are available in approximately 10 minutes. Vaginal culture is more sensitive than the direct microscopy of vaginal secretions, as it will detect up to 50% of even asymptomatic vaginal infections. Vaginal fluid should be screened microscopically for *Trichomonas vaginalis* in patients with signs and symptoms of vaginitis and in women with an increased risk of preterm birth.

## EFFECT ON PREGNANCY AND NEONATES

Infection with *Trichomonas vaginalis* has been associated with an increased risk of preterm delivery, premature rupture of membranes, and maternal puerperal morbidity.<sup>79–81</sup> However, data do not suggest that metronidazole treatment results in reduction in perinatal morbidity. Some trials even suggest the possibility of increased prematurity or low birth weight after metronidazole treatment. Limitations of the studies prevent definite conclusions regarding risk of treatment.<sup>82</sup> Treatment of *T. vaginalis* might relieve symptoms of vaginal discharge in pregnant women and might prevent respiratory or genital infection of the newborn and further sexual transmission. Clinicians should counsel patients regarding the potential risk and benefits of treatment. Some specialists would defer therapy in asymptomatic pregnant women until after 37 weeks gestation. In addition, pregnant women should be provided careful counseling regarding condom use and the continued risk of sexual transmission.

Neonatal infection with *Trichomonas vaginalis* is detected very infrequently. The vaginal mucosa of female neonates is susceptible to infection or colonization with *Trichomonas* due to the maternal estrogenic influence. However, this is reversed within 3–4 weeks after birth. Purulent vaginitis and urinary tract infection have been reported in neonates born to untreated mothers.<sup>83</sup>

## TREATMENT

Women may be treated with 2 g of metronidazole or Tinidazole in a single dose orally. Alternative regimen is metronidazole 500 mg orally twice daily for 7 days. Metronidazole is pregnancy category B drug. Multiple studies and meta-analyses have not demonstrated a consistent association between metronidazole use during pregnancy and teratogenic or mutagenic effects in infants.<sup>84–86</sup> Tinidazole in pregnancy is category C drug and its safety in pregnant women has not been well-evaluated.

In lactating women who are administered metronidazole, withholding breastfeeding during treatment and for 12–24 hours after the last dose will reduce the exposure of metronidazole to the infant. While using tinidazole, interruption of lactation is recommended during treatment and for 3 days after the last dose.

## Chlamydia Trachomatis

*Chlamydia trachomatis* is an obligate intracellular bacterium that has several serotypes, including those that cause lymphogranuloma venereum. The most commonly encountered strains are those that attach only to columnar or transitional cell epithelium and cause cervical infection. *Chlamydia trachomatis* is one of the most common sexually transmitted pathogens in the obstetric population, with 2–20% of the pregnant women being infected.<sup>87</sup> In Canada, a major increase in reported chlamydial infections occurred between 1984 (3.2 cases per 100,000) and 1994 (188 cases per 100,000), probably reflecting the improved screening and reporting.<sup>88</sup> *C. trachomatis* infections result in significant morbidity with concomitant social and economic costs. Left untreated, an affected pregnant patient may: (i) pass the organism to her baby at delivery, (ii) develop postpartum endometritis, salpingitis leading to pelvic inflammatory disease, ectopic pregnancy, and infertility (iii) contribute to horizontal spread throughout the community, and (iv) experience possible adverse obstetric outcomes such as preterm delivery, low birth weight, or premature rupture of membranes.<sup>89–93</sup> Debate exists regarding screening for chlamydial infection during pregnancy. National Institute for Health and Clinical Excellence Guidelines of UK<sup>94</sup> do not recommend chlamydial screening during pregnancy whereas the US guidelines do.<sup>95</sup>

### DIAGNOSIS

Diagnosis of *Chlamydia trachomatis* infection in women can be made by testing urine or swab specimen collected from endocervix or vagina. Culture, direct immunofluorescence, EIA, nucleic acid hybridization tests, and NAATs are available for the detection of *Chlamydia trachomatis* on endocervical and male urethral swab specimens.<sup>49</sup> NAATs are the most sensitive tests for these specimens and are FDA cleared for use with urine and some tests are cleared for use with vaginal swab specimens.

### PERINATAL TRANSMISSION

Infection in the mother is mostly subclinical or asymptomatic but at times may cause severe clinical syndromes that include urethritis, mucopurulent cervicitis, and acute salpingitis.

Vertical transmission of *C. trachomatis* generally occurs during labor and delivery with a frequency varying from 23% to 70%. The high prevalence of neonatal conjunctivitis (11–50%) and neonatal pneumonia (3–16%) has been reported among infants exposed at birth.<sup>96–98</sup>

### TREATMENT

Doxycycline, ofloxacin, and levofloxacin are contraindicated in pregnant women. However, clinical experience and studies suggest that azithromycin is safe and effective.<sup>99–101</sup> Repeat testing (preferably by a NAAT) 3 weeks after completion of therapy is recommended for all pregnant women to ensure cure, considering the sequelae that might occur in the mother

and neonate if the infection persists. Recommended regimen is Azithromycin 1 g orally in a single dose or amoxicillin 500 mg orally three times a day for 7 days. Alternate regimens are erythromycin base 500 mg orally four times a day for 7 days or erythromycin base 250 mg orally four times a day for 14 days or erythromycin ethylsuccinate 800 mg orally four times a day for 7 days or erythromycin ethylsuccinate 400 mg orally four times a day for 14 days. Erythromycin estolate is contraindicated during pregnancy because of drug-related hepatotoxicity. The frequent gastrointestinal side effects associated with erythromycin might discourage patient compliance and may require alternate regimens. The lower dose of erythromycin for 14 days may be considered if gastrointestinal tolerance is a concern. In countries where the drug is available, josamycin seems safe and efficacious and might also be considered.<sup>102,103</sup>

## Hepatitis B Virus

Hepatitis B virus (HBV) is endemic in many parts of the world particularly in Asia, South America, Southern Europe, and Africa.<sup>104</sup> This infection is a major cause of acute hepatitis as well as its serious sequelae, namely chronic hepatitis, cirrhosis, and hepatocellular carcinoma. The course of hepatitis B infection in the mother does not seem to be altered by pregnancy. Fulminant hepatitis may occasionally complicate hepatitis B infection but it does not seem to be more prevalent during pregnancy.

Sexual transmission is the most common mode of transmission in addition to infection by transfusion of blood and its products and intravenous drug use. Sexual transmission accounts for most adult HBV infections in the US.<sup>105</sup> Approximately 25% of the regular sexual contacts of infected individuals will become seropositive.<sup>106</sup>

10–20% of women seropositive for HBsAg transmit the virus to their neonates in the absence of immunoprophylaxis. In women who are seropositive for both HBsAg and HBeAg, vertical transmission is approximately 90%.<sup>106</sup> In patients with acute hepatitis B, in the first trimester vertical transmission occurs in up to 10% of neonates, and in 80–90% of neonates when it occurs in the third trimester.<sup>106</sup>

HBV infection does not appear to cause birth defects, but there appears to be a higher incidence of low birth weight among infants born to mothers with acute infection during pregnancy.<sup>107</sup> In one small study acute maternal hepatitis (type B or nontype B) had no effect on the incidence of congenital malformations, stillbirths, abortions, or intrauterine malnutrition. However, acute hepatitis in the mother did increase the incidence of prematurity.<sup>108</sup>

The presence of HBsAg indicates ongoing HBV infection, and in newly infected persons, HBsAg is the only serologic marker detected during the first 3–5 weeks after infection. In persons who recover from HBV infection, HBsAg is usually eliminated from the blood in 3–4 months, and anti-HBs antibodies develop.<sup>109</sup>

Pregnancy is not a contraindication to vaccination. When exposed to a person who has active hepatitis B infection, pregnant patient should receive vaccination as well as immune globulin. When exposed to a person with chronic HBV infection, only



vaccination is required. Babies born to hepatitis B carriers should receive hepatitis vaccine and hepatitis B immune globulin (HBIG) within 12 hours of birth.

## SCREENING

All pregnant women should be tested for hepatitis B surface antigen at first prenatal visit. Women admitted for delivery who have not had prenatal HBsAg testing should have blood drawn at delivery for testing.<sup>109</sup> Routine follow-up testing later in pregnancy is not necessary except in special circumstances such as exposure to a patient with hepatitis or a patient with high-risk behavior (parenteral drug abuse).<sup>110</sup>

## TREATMENT

The treatment of acute HBV infection is supportive. Patients should be hospitalized if they have coagulopathy, encephalopathy, or severe debilitation.

Persons with chronic hepatitis B should be referred to healthcare professionals with experience in the treatment of hepatitis B with alpha-interferon or lamivudine. Interferon does not appear to adversely affect the embryo or fetus. However, the data is limited, and the potential benefits of interferon use during pregnancy should clearly outweigh possible hazards.<sup>111–113</sup> Initial data do not suggest that lamivudine is teratogenic.<sup>114</sup> Lamivudine has been used in the latter half of pregnancy in an attempt to prevent perinatal transmission of hepatitis B virus infection with mixed success.<sup>115,116</sup>

## DELIVERY

Although cesarean delivery has been proposed as a means of reducing mother-to-child transmission of HBV,<sup>117</sup> the mode of delivery does not appear to have a significant effect on the interruption of HBV maternal-baby transmission when vaccine and passive immune globulin is given.<sup>118</sup> Delivery by cesarean section for the purpose of reducing mother-to-child transmission of HBV is not presently recommended by either the CDC<sup>105</sup> or the ACOG.<sup>106</sup>

## BREAST FEEDING

With appropriate hepatitis B immunoprophylaxis, breast-feeding poses no additional risk for transmission from infected hepatitis B virus carrier mothers.<sup>119,120</sup>

## Herpes Simplex Virus

Two types of herpes simplex virus (HSV) have been distinguished based on immunological differences. Type 1 is responsible for most non-genital herpetic infections but frequently involves the genital tract. Type 2 virus is recovered almost exclusively from the genital tract and is transmitted in most of the instances by sexual contact. The incidence of antibodies specific for type 2 herpes virus increases with age and varies considerably with the population studied.

Five percent of all women of childbearing age report a history of genital herpes, and up to 30% have antibodies to herpes simplex virus 2 (HSV-2). 2% of women acquire genital HSV during pregnancy. The incidence of neonatal herpes varies considerably in international studies (about 1:3200 births in the US and 1:60,000 in the UK). Untreated neonatal HSV infection is associated with a mortality of 60%, and even with early and appropriate treatment, survivors experience considerable disability.<sup>121</sup>

## CLINICAL FEATURES AND COURSE DURING PREGNANCY

With primary infection, the typical incubation period of 3–6 days is followed by a papular eruption with itching or tingling which then becomes painful and vesicular with multiple vulvar and perineal lesions that may coalesce. Inguinal adenopathy may be severe. Transient systemic influenza-like symptoms are common and are presumably caused by viremia. Occasionally hepatitis, encephalitis, or pneumonia may develop. Freiden et al. in 1990 reported six cases of maternal encephalitis complicating pregnancy, only two women survived.<sup>122</sup> Although commonly involved in primary disease, cervical involvement is less frequent with recurrent infections.<sup>123,124</sup> Subclinical shedding of HSV-2 occurred in 55% of patients during a mean follow-up of 105 days and lasted for a mean of 1.5 days and often followed a symptomatic recurrence.<sup>125</sup>

Asymptomatic viral shedding is episodic and brief, usually lasting 24–48 hours. 1–2% of pregnant women with a history of recurrent HSV infection have asymptomatic shedding at the time of delivery. Co-infection with HIV may increase asymptomatic shedding of HSV.<sup>126</sup>

Approximately, 80% of young women with recently acquired genital herpes infection will have an average of 2–4 symptomatic recurrences during pregnancy.<sup>123–127</sup> Concomitant cervical shedding is identified in about 15% of women with clinically evident vulvar recurrences. Approximately 10% of the recurrences in pregnancy are asymptomatic, and these are more frequently around the perineum than the cervix. The incidence of positive cultures at any time during pregnancy or at delivery for women who had herpes during non-pregnant time is only 1–2%. Although clinical recurrences appear to be slightly more common in late pregnancy, asymptomatic cervical shedding of herpes virus is unaffected by the duration of pregnancy. Additionally, “remote recurrences,” that is, those on the buttocks, back, thigh, and anus, have low rates of concomitant cervical virus shedding and this safely allows consideration for vaginal delivery.<sup>124–127</sup>

## PERINATAL TRANSMISSION OF HSV

HSV can be vertically transmitted to the infant before, during, or after delivery, although intrapartum transmission accounts for most cases. Maternal age of less than 21 years is a risk factor for vertical transmission.<sup>128</sup>

Approximately 5% of all cases of neonatal HSV infection result from *in utero* transmission. With primary infection, hematogenous spread can produce a spectrum of findings such

as microcephaly, microphthalmia, intracranial calcifications, and chorioretinitis.

Intrapartum transmission accounts for most neonatal infections and occurs with passage of the infant through an infected birth canal. The use of a fetal-scalp electrode increases the risk for intrapartum transmission.<sup>128</sup> From 75% to 90% of infants with neonatal HSV are born to infected asymptomatic mothers who have no known history of genital HSV. Postnatal transmission of HSV can occur through contact with infected parents or healthcare workers.

## NEONATAL INFECTION

Newborn infection has three forms: disseminated, localized, and asymptomatic. Nearly 50% of infected neonates are preterm and their risk of infection correlates with whether there is primary or recurrent maternal infection. Nahmias et al. reported a 50% risk of neonatal infection with primary maternal infection but only 4–5% with recurrent infection and the rates being in between with non-primary first episode.<sup>129</sup> Localized infection is usually associated with a good outcome. Conversely, even after treatment with acyclovir or vidarabine, disseminated neonatal infection is associated with a mortality of at least 60%. Significant serious ophthalmic and CNS damage has been identified in at least 50% of the survivors.<sup>130</sup>

## DIAGNOSIS

HSV culture has long been the criterion standard for diagnosis of HSV infection, with a sensitivity of 70% and a specificity of nearly 100%. The Tzanck smear is an older test that is no longer used because of the large number of both false-positive and false-negative results. Polymerase chain reaction (PCR) is a molecular test that is being increasingly used and that may ultimately replace HSV culture as the standard.<sup>131–133</sup>

## ANTIVIRAL THERAPY

Acyclovir, a nucleoside analogue, was the first antiviral therapy approved for the treatment and prevention of HSV infection. Valacyclovir and famciclovir have been labeled as category B drugs. Recommended regimens for first clinical episode of genital herpes is:

Acyclovir 400 mg orally three times a day for 7–10 days  
OR Acyclovir 200 mg orally five times a day for 7–10 days  
OR Famciclovir 250 mg orally three times a day for 7–10 days  
OR Valacyclovir 1 g orally twice a day for 7–10 days.

Recommended regimen for episodic therapy for recurrent genital herpes is Acyclovir 400 mg orally three times a day for 5 days  
OR Acyclovir 800 mg orally twice a day for 5 days  
OR Acyclovir 800 mg orally three times a day for 2 days  
OR Famciclovir 125 mg orally twice daily for 5 days  
OR Famciclovir 1000 mg orally twice daily for 1 day  
OR Valacyclovir 500 mg orally twice a day for 3 days  
OR Valacyclovir 1.0 g orally once a day for 5 days.

In 1984, the manufacturer of acyclovir, in conjunction with the CDC, established a registry monitoring the safety of the drug.

The registry was closed in 1999. In that time, 1129 acyclovir-exposed pregnancies were reported to the registry; 712 of these occurred in the first trimester. Additionally, 56 valacyclovir-exposed pregnancies were reported; 14 of these occurred in the first trimester.

No increase in the number of malformations occurred with acyclovir, and no pattern of birth defects emerged. Too few cases of valacyclovir-exposed pregnancies precluded the drawing of any meaningful conclusions. Thus, acyclovir appears to be relatively safe to use during pregnancy and should be prescribed as medically indicated.

Proposed 2010 European Guidelines for management of genital herpes also state that women with first episode genital herpes should be treated in line with her clinical condition and will often involve the use of either oral or intravenous acyclovir in standard doses. For recurrent HSV in early pregnancy continuous or episodic therapy is not recommended and should be avoided. Clinicians are on occasion obliged to use therapy for severe and complicated disease and a case-by-case assessment should be made. Newer antivirals should be avoided and the dose of acyclovir titrated down to the minimum effective level.<sup>134</sup>

## STRATEGIES TO PREVENT VERTICAL HSV TRANSMISSION

### Antiviral Suppression for Gravidas with First-Episode Infections during Pregnancy

Scott et al. randomized 46 gravidas with first genital outbreak during pregnancy to receive either acyclovir (400 mg tid) or placebo beginning at 36 weeks' gestation. Patients receiving acyclovir experienced a significant reduction in the percentage of HSV recurrences at delivery (36% vs. 0%) and cesarean deliveries for HSV (36% vs. 0%).<sup>135</sup>

### Antiviral Suppression for Gravidas with a History of Genital HSV

In 1998, Brocklehurst and colleagues performed a double-blind placebo-controlled trial that involved 63 women with a history of recurrent HSV infection.<sup>136</sup> These women were randomized to receive either acyclovir (200 mg qid) or placebo, both beginning at 36 weeks' gestation. No infant in either group developed neonatal HSV, and no gravida experienced toxicity from acyclovir. A 2003 meta-analysis in 799 gravidas also showed that after suppressive therapy there was significant decrease in recurrent HSV infection at delivery, caesarean deliveries for HSV and asymptomatic HSV shedding at delivery.<sup>137</sup> Cochrane Database of Systematic Reviews 2008 (which included 1249 participants) concluded that women with recurrent genital herpes simplex virus should be informed that the risk of neonatal herpes is low. There is insufficient evidence to determine if antiviral prophylaxis reduces the incidence of neonatal herpes. Antenatal antiviral prophylaxis reduces viral shedding and recurrences at delivery and reduces the need for cesarean delivery for genital herpes.

Limited information exists regarding the neonatal safety of prophylaxis. The risks, benefits, and alternatives to antenatal prophylaxis should be discussed with women who have a history and prophylaxis initiated for women who desire intervention.<sup>138</sup>

In 2007, the ACOG published a practice bulletin regarding HSV in pregnancy.<sup>139</sup> Their conclusions were as follows:

- Women with active, recurrent genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation.
- Cesarean delivery is indicated in women with active genital lesions or prodromal symptoms
- Routine HSV screening of pregnant women is not recommended.

## Human Papillomavirus Infection

Anogenital warts are caused by the human papillomavirus (HPV) of which many subtypes have been identified. The subtypes most commonly associated with the genital warts are types 6 and 11, but warts may also be caused by oncogenic types 16 and 18.<sup>140</sup> Women appear to be more likely to manifest HPV infection as symptomatic warts during pregnancy than at other times. Warts are the only manifestation of HPV infection but many women (and men) are infected with HPV in the genital area and will never develop warts. The prevalence of HPV infection in pregnant women has been variously estimated at 5–15%.<sup>141–144</sup> It has been demonstrated that HPV can be transmitted from mother-to-child although the full clinical significance of this for the child is relatively poorly understood.<sup>145</sup> Anogenital warts and juvenile laryngeal papillomatosis are better recognized.<sup>146</sup>

Juvenile onset recurrent respiratory papillomatosis (JORRP) is a benign condition caused by human papillomavirus, usually subtypes 6 and 11 and presents as papilloma in the respiratory tract from the nasal vestibule to the lung tissue in infants and children. Hoarseness of voice and symptoms of obstruction of upper airway tract are the presenting features. Maternal condyloma is the usual source of infection and is found in 50% of the mothers giving birth to JORRP babies.<sup>147</sup> A recent retrospective cohort study has shown that children born to mothers with a history of genital warts have a 231.4 times higher risk of JORRP than those with no such history. In women with genital warts, delivery time of more than 10 hours was associated with a two-fold greater risk of disease. Cesarean delivery was not found to be protective against JORRP.<sup>148</sup>

Oligonucleotide probes specific to each of the five HPV strains have been used to prove the consonance of maternal virus and virus in the newborn. A study on 301 pregnant women with papilloma virus reported that the overall transmission for 16/18 type virus was 40%. The rate was significantly higher for those delivered vaginally compared with caesarean deliveries (51% vs. 27%).<sup>149</sup> A 30% transmission rate of the virus to the oropharynx of the neonates has been reported in another study; it also showed that the virus was cleared by five weeks.<sup>150</sup> Manns documented that only 3% of infants were seropositive to HPV-16 by 1–2 years.<sup>151</sup>

## CLINICAL COURSE DURING PREGNANCY

For reasons not fully known, genital warts frequently increase in number and size during pregnancy, sometimes filling the vagina or covering the perineum and making it difficult to perform vaginal delivery or episiotomy. Certainly, the vaginal mucus throughout pregnancy offers ideal moist conditions for viral growth. Accelerated viral replication with advancing pregnancy has been hypothesized to explain the growth of perineal lesions, progression of some to cervical neoplasm, and the increased detection of viral DNA from the cervix of pregnant women.<sup>152</sup> Because papilloma virus infection can be subclinical and multifocal, most women with vulvar lesions also have cervical infection, and vice versa.<sup>153</sup> Vulvar lesions often improve rapidly or disappear in the postpartum period, possibly related to the loss of either vascularity, excessive moisture or the alleged immunosuppression of pregnancy.

## SCREENING AND PREVENTION

The human papillomavirus (HPV) vaccine may prevent infection with certain serotypes of human papillomavirus associated with the development of cervical cancer, genital warts, and some other less common cancers.<sup>154,155</sup> Two HPV vaccines are currently in the market: Gardasil and Cervarix.<sup>156</sup> Both vaccines protect against two of the HPV types (HPV-16 and HPV-18) that can cause cervical cancer and some other genital cancers; Gardasil also protects against two of the HPV types that cause genital warts.<sup>154</sup>

Public health officials in Australia, Canada, Europe, and the US recommend vaccination of young 9–26 years women against HPV to prevent cervical cancer and genital warts

In the Gardasil clinical trials, 1115 pregnant women received the HPV vaccine. Overall, the proportions of pregnancies with an adverse outcome were comparable in subjects who received Gardasil and subjects who received placebo.<sup>157</sup> However, the clinical trials had a relatively small sample size. Currently the vaccine is not recommended for pregnant women.<sup>154–157</sup>

## TREATMENT

There are relatively few randomized controlled trials of the effectiveness of various treatment regimens for anogenital warts and there appear to be none conducted on pregnant women. Many treatment regimens that are effective in nonpregnant women are suitable for use in pregnancy, except cytotoxics like podophyllin, or podophylotoxin that should be avoided because of a theoretical risk of teratogenicity. The aim of the treatment is to destroy the wart tissue and, although most treatments are effective, this tissue destruction is not necessarily associated with the eradication of HPV. It has not been determined whether transmission to the neonate from the normal intact skin infected with HPV is less than from symptomatic warts. Effective treatments include cryotherapy, cauterization with trichloroacetic acid, excision, electrocautery, and laser therapy. Recurrences after therapy are common. During pregnancy,



the growth of anogenital warts can occasionally become very rapid and treatment may have to concentrate on a strategy of maintaining the status quo rather than the complete removal of the warts. Very rarely, if neglected, anogenital warts can become so large that they may obstruct vaginal delivery in which case a caesarean section is indicated.

## Granuloma Inguinale (Donovanosis)

Granuloma inguinale is a genital ulcerative disease caused by the intracellular gram-negative bacterium *Klebsiella granulomatis* (formerly known as *Calymmatobacterium granulomatis*). It is endemic in some tropical and developing areas, including India, Papua New Guinea, central Australia, and southern Africa. Clinically, the disease is commonly characterized as painless, progressive ulcerative lesions without regional lymphadenopathy. The lesions are highly vascular (i.e., beefy red appearance) and bleed easily on contact. However, the clinical presentation also can include hypertrophic, necrotic or sclerotic varieties. The causative organism is difficult to culture, and diagnosis requires visualization of dark-staining Donovan bodies on tissue crush preparation or biopsy.

## Clinical Course During Pregnancy

The lesions of donovanosis tend to proliferate or recur and show diminished response to standard antimicrobial therapy.<sup>158–161</sup> The cervical lesions may rapidly enlarge, extend to the pelvic structures, and disseminate resulting in fatal hemorrhage at the time of delivery.<sup>162,163</sup> This is due to increased vascularity of the lesions and the immunosuppressive effect of pregnancy.<sup>164</sup> Hypertrophic variant is more commonly seen in pregnancy.<sup>165</sup> However, in a recent study there was no difference in the type of lesions and response to therapy in patients with and without pregnancy.<sup>162</sup>

## Perinatal Transmission

This has been reported occasionally. The lesions reported in neonates and infants, probably due to vertical transmission in mothers with untreated donovanosis, include suppurative otitis media, cervical lymphadenopathy, and lesions on the umbilicus, labia, and penis.<sup>163–167</sup>

## Treatment

A limited number of studies on Donovanosis treatment have been published. Treatment halts progression of lesions, although prolonged therapy is usually required to permit granulation and re-epithelialization of the ulcers. Healing typically proceeds inward from the ulcers margins. Relapse can occur 6–18 months after apparently effective therapy. Several antimicrobial regimens have been effective, but a limited number of controlled trials have been published.<sup>168</sup> Doxycycline 100 mg orally twice a day for at least 3 weeks and until all lesions have healed completely is the recommended regimen.

## Alternative Regimens

Azithromycin 1 g orally once a week OR Ciprofloxacin 750 mg orally twice a day OR Erythromycin base 500 mg orally four times a day OR Trimethoprim-sulfamethoxazole one double-strength (160 mg/800 mg) tablet orally twice a day. All therapies should be continued at least 3 weeks or until all lesions have completely healed. Some specialists recommend the addition of an aminoglycoside (e.g., gentamicin 1 mg/kg IV every 8 hours) to these regimens if improvement is not evident within the first few days of therapy.

Pregnancy is a relative contraindication to the use of sulfonamides, doxycycline, and ciprofloxacin. Pregnant and lactating women should be treated with the erythromycin regimen and consideration should be given to the addition of a parenteral aminoglycoside (e.g., gentamicin). Azithromycin might prove useful for treating granuloma inguinale during pregnancy, but there are few published data.

## Conclusion

STIs are common infections of young people in the reproductive age group. During pregnancy these infections not only affect the maternal health but also have significant effect on their reproductive outcome (abortion, preterm birth, stillbirth congenital infection and postpartum infection, ectopic pregnancy, and infertility).

Women with STIs may not have symptoms and may not know the significance of their not very distressing symptoms during pregnancy. Screening all women during pregnancy at the first prenatal visit and repeat screening in 3rd trimester or at labor (for women not tested in prenatal time) provides a good opportunity to detect these infections and treat them during pregnancy.

Most of the recommended treatment regimens in pregnant women do not differ from those for the non pregnant women.

Pregnancy provides an excellent window of opportunity to obstetricians to screen the women and treat them with appropriate regimen in whom infection is diagnosed.

Obstetricians also have a good opportunity to counsel their women for preventive measures, like use of condoms and avoidance of high risk behavior. All these measures can go a long way to help the woman, her partner, the new born, and the society at large.

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# 91

## Sexually Transmitted Infections in Neonates and Infants

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### Introduction

Sexually transmitted infections (STIs) in infants and newborns can follow vertical transmission during pregnancy or delivery, or rarely be acquired from external source, non-sexual contact post-delivery. *In utero* infections occur from placental spread, and these include syphilis or cytomegalovirus (CMV). Ascending infections causing chorioamnionitis may follow premature rupture of membranes (PROM). An infected birth canal during delivery is the source of other infections such as herpes simplex virus, HIV, Hepatitis B, human papilloma virus, gonorrhoea, and *Chlamydia trachomatis* (CT). Post-natal infections occur from breastfeeding (HIV) or may follow transmission from an exogenous source (Herpes simplex). The high incidence of STIs in the adult population in developing countries generally correlates with the high frequency of congenital syphilis and ophthalmia neonatorum (ON) reported from these countries.<sup>1</sup>

STI control is particularly compelling because of its reproductive sequelae, fetal wastage, prematurity, and other complications caused by STIs especially in the developing countries.

Neonatal infections are those defined as occurring in the first month of life. It is at this time, particularly in neonates of low birth weight, there will be diminished efficacy of immune function. Maximal maternal protective immunoglobulin crosses the placenta late in gestation and the amount will be limited depending on the degree of prematurity. Therefore the increased susceptibility of the premature neonate to all these infections can be easily understood.

### STIs in Newborns

Neonatal conjunctivitis or ON from gonorrhoea has been well documented since 1882 as a cause of blindness. This initiated successful use in some countries, of Crede ocular prophylaxis at birth. It is now known that conjunctivitis is often more commonly caused by CT and this does not respond to ocular prophylaxis with silver nitrate.<sup>2</sup> STIs in the neonate can include trichomoniasis, herpes simplex viruses 1 and 2, human papilloma virus, CMV, the hepatitis B, C, G virus as well as other bacterial

infections including *Streptococcus agalactiae* (Group B Strep). The latter is associated with bacterial vaginosis (BV), which along with mycoplasmas, (also part of the mixed bacterial flora of BV) have been shown to be associated with amnionitis and preterm delivery.<sup>3</sup> Of the commonly considered congenital infections, CMV, syphilis, and herpes simplex virus are the ones most commonly transmitted from the mother.

### GONORRHOEA

The incidence of gonorrhoea in pregnant women has varied from rare to 10%. The chief manifestation in the newborn is conjunctivitis. Other manifestations include meningitis (fatal fulminating meningitis with Waterhouse–Friderichsen syndrome and adrenal hemorrhage), endocarditis, gonococcal septicemia, arthritis, scalp abscess, vaginitis, urethritis, retinitis, proctitis, and funisitis (inflammation of the umbilical cord).<sup>4</sup>

### Epidemiology of Gonorrhoea

Information on the prevalence of gonococcal infection in the neonatal period is limited. The estimated incidence, 6.5 per 100,000 population, was reported from USA<sup>4</sup> in the 1980s. Gonococcal infection of the newborn occurs by vertical transmission from the infected mother during delivery. Contamination of the fetus may also occur *in utero* if there is early rupture of membranes and amnionitis.<sup>5</sup> Scalp abscesses following attachment of probes for fetal monitoring have been described.<sup>6</sup> The estimated rate of transmission from the infected mother to the newborn varies from 30% to 50%.<sup>7–9</sup>

Maternal gonococcal infection has been associated with a statistically greater occurrence of PROM, prolonged rupture of membranes, chorioamnionitis, and premature delivery.<sup>9</sup>

### Gonococcal Neonatal Conjunctivitis

Symptoms may present a few hours after birth in cases where there has been delay between the PROM and delivery up to 2–3 weeks.<sup>10</sup> The disease presents as a mucopurulent discharge





**Fig. 91.1:** Gonococcal ophthalmia neonatorum. *Courtesy:* Dr. BSN Reddy and Sujay Khandpur, New Delhi, India.

that literally pours out when the eyelids are separated, both eyes are nearly always affected (Fig. 91.1). The conjunctivae become intensely inflamed, bright red and swollen with marked chemosis. There is a dense infiltration of the bulbar conjunctiva initially that later becomes puckered and velvety with free discharge of pus, serum, and blood. A false membrane may form in a few cases resembling membranous conjunctivitis. Untreated cases develop corneal ulcers over an oval area just below the centre of the cornea. Rarely marginal ulcers may form followed by corneal perforation, iris prolapse, and extrusion of the lens.

Other complications include anterior synechiae, adherent leukoma, partial or total anterior staphyloma, anterior capsular cataract, and panophthalmitis. Macular fixation may be impaired causing nystagmus.

Local or systemic spread may occur resulting in oropharyngeal gonorrhoea in approximately 35% of cases, and meningitis and/or arthritis may develop. Joint manifestations usually appear in the third to fourth week and affect the knee, wrist, ankle, and elbow joints.<sup>11,12</sup>

### Laboratory Diagnosis

Culture is still more of a gold standard than polymerase chain reaction (PCR) and nucleic acid amplification tests (NAATs), which can give false positive results from commensal *Neisseria*.<sup>8</sup> Optimal isolation is by direct plating and immediate incubation in 5% CO<sub>2</sub>. Identification requires biochemical, serological, and enzyme substrate tests. The routine testing of sugar utilization is positive for glucose but not maltose, lactose or sucrose. *Neisseria meningitidis* has been described in neonatal conjunctivitis as well as other *Neisseria* species so that at least two types of identification methods are necessary.

**Nucleic Acid Amplification Tests for *N. Gonorrhoea*** These have been shown to be diagnostic. In the past, Amplicor (PCR) test gave false results with *Neisseria subflava* and *N. cinerea*.<sup>13</sup>

The CDC 2010 guideline includes the use of NAATs for the diagnosis of *N. gonorrhoeae* (NG) in children, using vaginal, urethral swabs, and urine. There is no approval as yet for the use of NAATs on throat or rectal swabs; cultures are indicated.

In a multicentric study to evaluate and compare nucleic acid amplification tests, with the standard culture technique, 485 female

children were investigated for infection. Prevalence of infection was 2.7% for chlamydia and 3.3% for *N. gonorrhoea*. Eight CT positive and four NG positive children with NAATs had culture negative results. The authors concluded that the Strand displacement amplification (SDA) and Transcription-mediated amplification (TMA) tests with confirmation by a different NAATs are adequate for use on urine samples as a new forensic standard for diagnosis of CT and NG in prepubertal girls suspected of sexual abuse. There has been no study in prepubertal boys. Other NAATs have been used regularly in the routine diagnosis of conjunctivitis. NAATs offer a clear advantage over culture in sensitivity and are less invasive, reducing patients' trauma and discomfort.<sup>14</sup>

### Treatment

Gonococcal ON is treated with Ceftriaxone 25–50 mg/kg IV or IM not exceeding 125 mg in a single dose. Alternative treatments for gonococcal infection in other sites can be cefotaxime 100 mg/kg IV or IM as a single dose. If there is disseminated gonococcal infection with arthritis or scalp abscess, ceftriaxone 25–50 mg/kg IV or IM is given daily for 7 days or cefotaxime 100–150 mg/kg/day IV or IM in three divided doses for 7 days. Meningitis may require treatment for 10–14 days and higher doses may be necessary.<sup>15</sup> Testing for CT should also be done concurrently. The parents of the child and/or other sex partners should be screened and appropriately treated. Occasionally, prophylactic treatment is indicated where mothers are known to have gonococcal infection and ceftriaxone can be used as above.

## Ophthalmia Neonatorum

A baby with purulent discharge from the eyes occurring within 21 days of birth is diagnosed to have ON.

In 1881, a Liverpool eye surgeon wrote that 60–75% of blindness in any large home for the blind was caused by ON. At the end of the 19th century in Europe the prevalence of ON among live births in maternity hospitals exceeded 10%. Corneal damage of the neonates developed in 20% and blindness in about 3% of the affected infants.<sup>16,17</sup> Blindness from ON is rare, especially in industrialized countries due to a low prevalence of STIs in pregnant women and prophylaxis at birth. Worldwide 1000–4000 new born babies become blind every year because of ON.<sup>18</sup>

In a recent study from Iran, 4021 neonates were examined for the presence of conjunctivitis and 198 (4.9%) were positive. Forty seven percent of the mothers of these babies had PROM and 11% had genitourinary infections. Most Common sexually transmissible causative organism was *N. gonorrhoeae* in 3% and *C. trachomatis* in 2%.<sup>19</sup> CT was detected by DFA staining in 31% of the 58 neonates with conjunctivitis in an Indian study.<sup>20</sup>

In 1998, the prevalence of gonococcal ON was reported as 0.04% in Belgium and Netherlands and 0.3 per 1000 live births in the USA.<sup>21</sup>

*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria cinerea*, *Moraxella catarrhalis*, and viruses such as herpes simplex and adenovirus can also be co-infections.<sup>5,21</sup>

A study in Kenya in 1986 showed that of 42% of 67 babies born to infected mothers, who were not given prophylaxis against ON developed ON.<sup>22</sup>

### Prevention of Ophthalmia Neonatorum

Antenatal care should include the screening of at-risk women and their adequate treatment and that of the partner(s) predelivery. A precautionary second screening late in pregnancy is advisable in women who are at high risk. Rothenberg's review of 24 studies using silver nitrate topically (Crede's method) post-delivery prevented ON in 99.94% of cases.<sup>23</sup> Alternative prophylactic antibiotic regimens have been tried because of the risk of chemical conjunctivitis from silver nitrate and erythromycin has been found to be efficacious in several studies as an ophthalmic ointment.<sup>24,25</sup> According to CDC guidelines, povidone-iodine installation prophylaxis may not be successful in premature neonates with PROM and gonococcal amnionitis.<sup>15</sup>

In children born to untreated mothers, in areas where the prevalence of maternal gonococcal infection is greater than 1%, or where maternal screening is not undertaken, a two-stage prophylaxis, Crede's method, is followed. In the first step, the eyelids and eyelashes of the infant are wiped free of pus or organic matter as soon as the head is delivered and before the eyes are opened, in the second stage after the child is born, one or two drops, of 1% aqueous silver nitrate are instilled into each eye. Silver nitrate may not prevent the infection which is already established. Conjunctival irritation from the silver nitrate can occur from 6 to 24 hours after use but the reaction resolves by 24–48 hours.<sup>5</sup>

In the United States, 1% tetracycline or 0.5% erythromycin ophthalmic ointment are recommended (CDC). Topical tetracycline prophylaxis has some effect but little effect on subsequent development of chlamydial pneumonia.<sup>26</sup>

According to Hammerschlag, the most effective method of control of perinatal CT infection is screening and treatment of pregnant women.<sup>8</sup>

## CHLAMYDIAL INFECTIONS

### Conjunctivitis

Neonatal chlamydial conjunctivitis has been reported to occur in 52–75% of infants born to mothers with cervical chlamydial infection.<sup>27,28</sup> In Bell's study analysis of the incidence post-caesarean section showed 20% to be infected even with intact membranes. The incubation period can be from 3 days in premature infants, but mostly is between the 6th day up to 13 days. Fifty percent of infants also have nasopharyngeal infection, 20% of these may develop neonatal pneumonia and the middle ear, gut, and vagina may be infected.<sup>29</sup> The conjunctivae are injected. There will be a copious watery discharge which can be mucopurulent. There is papillary hyperplasia of the conjunctivae with swelling of the eyelids. Bilateral infections may be present in two-thirds of cases.<sup>30</sup> Occasionally, gonococcal neonatal conjunctivitis is

co-existent, but the relatively earlier incubation period should alert the clinician. The increased incidence of chlamydial neonatal conjunctivitis compared to gonorrhoea would indicate treatment for both. Most cases of chlamydial D-K infections are benign, some are even asymptomatic. But there are reports of micropannus formation and occasional scarring.<sup>31</sup>

### Chlamydial Pneumonia

Lower respiratory tract infection in the form of an atypical pneumonitis may follow in a 6th of babies born with conjunctivitis, particularly if systemic antibiotics are not used in treatment of the latter. Per nasal swab culture may confirm the diagnosis of nasopharyngeal infection, but often the infection is missed as this can present 3 weeks to 3 months post-delivery. Apnoeic attacks are frightening for the mother and the child may have a "staccato" cough. Patchy signs may be present on chest X-ray, and eosinophilia and increased immunoglobulins on blood testing. A positive chlamydia micro-immunofluorescence (MIF) test may be helpful with an IgM titer of 1:16 or more. It is not yet clear if *C. trachomatis* pneumonitis is associated with chronic lung disease.

Other infections with similar presentations include respiratory syncytial virus and *Mycoplasma pneumoniae*.<sup>32</sup> Infants with chlamydial pneumonia have also been described with middle ear infection, serous otitis media,<sup>33</sup> which may lead to middle ear infection in older children.<sup>13</sup>

### Laboratory Diagnosis

The Giemsa stain of a conjunctival scraping for the characteristic basophilic intracytoplasmic inclusions may be helpful. Culture on McCoy cells from conjunctival scrape swabs has been the mainstay or gold standard of diagnosis. CDC has approved the use of enzyme immunoassays and direct fluorescent antibody test in the past for the diagnosis of chlamydial conjunctivitis. Tests generally approved by CDC include PCR, SDA, and TMA NAATs (their use on pharyngeal and rectal swabs is still being assessed).

PCR for conjunctival swabs gave a sensitivity of 92.3% and specificity of 100%. Other NAATs have not been adequately tested from this site but are used.<sup>34</sup>

### Treatment of Chlamydial Infections

Systemic treatment for chlamydial ON should be offered in the form of oral erythromycin base or ethyl succinate for 14 days, topical therapy is not indicated. Erythromycin is given as four divided doses of 50 mg/kg/day orally. Up to 80% of infants respond but a second course of treatment sometimes has to be given. Mothers and their sexual partners should also be screened and appropriately treated. Similarly in cases of pneumonia, the treatment is for 14 days with erythromycin at 50 mg/kg/day divided into four doses. Again a further course of erythromycin may be indicated as 20% may not respond fully to the initial course.<sup>15,35</sup>

## Trichomonas Vaginalis

Risk of neonatal trichomoniasis is increased in children born with low birth weight, preterm delivery and PROM. This motile protozoan is transmitted through an infected birth canal. Carriage and/or infection are recorded post delivery up to the 19th day.

The vaginal epithelium of the infant is thought to be prone to the infection while maternal estrogen is present. Estrogen causes epithelial thickening, there is a lower vaginal pH and more glycogen, but this is transient. The infection may be asymptomatic or present with a purulent vaginal discharge, pyuria may be found and the respiratory tract may be involved. However, usually the infection is very transient and probably missed.

A study of 984 neonates included 333 swabbed and/or cultured for *Trichomonas*; 0.1% were diagnosed on microscopy, and 0.6% more were detected where culture was used.<sup>36</sup> Respiratory distress has been reported where *T. vaginalis* has been isolated from nasal secretions.<sup>37</sup> A 2 week old girl with herpes encephalitis and respiratory symptoms responded to Metronidazole after *T. vaginalis* was isolated from a nasopharyngeal wash. The organism was diagnosed by PCR, typical electron microscopy appearance, and on cloning was identified as *T. vaginalis* rather than *T. tenax*.<sup>38</sup>

## NEONATAL HERPES SIMPLEX VIRUS INFECTION

About 50–80% of neonatal herpes simplex virus (HSV) infections are caused by HSV 2.<sup>39</sup> HSV infection of the newborn can be acquired in three ways. Intrauterine infections (approximately 5%) can occur as a consequence of either transplacental or ascending infection. The most common mode of infection (80–90%) is by contact with infected maternal genital secretions during birth. The third method of infection is postnatally (10–15%).

The duration and quantity of viral shedding and time to healing in the mother varies with whether it is a primary infection or a non-primary first episode or recurrent (HSV1 and HSV2). These are the major factors that influence the frequency of transmission and perhaps the severity of neonatal infection. The mother's antibody status to HSV at delivery appears to be an additional factor that also influences the severity of infection as well as the likelihood of transmission.

The risk of acquiring neonatal HSV infection from a recurrent maternal infection is about 0.05% from women who are asymptomatic at vaginal delivery. However, if they have symptomatic clinical disease at delivery, the risk of transmission is 0.25–3%.<sup>40</sup> In a large study, HSV culture and serum samples were obtained at the time of delivery. HSV was isolated from the birth canal of 202 women and 5% of their babies had acquired infection.<sup>41</sup>

The risk of acquisition from primary HSV infection at delivery is up to 57%, while vertical transmission rates of 25% are found in those with a non-primary first episode (infection with one virus type in the presence of antibody to the other virus type). However, most infants with neonatal HSV are born to mothers

with no history of symptomatic genital herpes at term. These women shed the virus asymptomatically.<sup>41,42</sup>

More than 2% of women seroconvert to HSV 2 during pregnancy. Neonatal HSV infection rates were 54/100,000 live births in HSV seronegative women, 26 among women who were HSV -1 seropositive only and 22 among HSV-2 seropositive.

Caesarean section reduced the HSV transmission significantly. Other risk factors for neonatal HSV included first episode maternal infection, HSV isolation from cervix at the time of labor, invasive monitoring, delivery before 38 weeks, maternal age less than 21 years and PROM.<sup>40</sup> Kropp reports an increasing number of neonatal herpes infections from HSV 1.<sup>43</sup>

## Intrauterine HSV Infection

Transmission before the 20th week of pregnancy can cause abortion in up to 25% of cases. Signs at delivery may include growth retardation, chorioretinitis, microcephaly/anencephaly, and skin scarring. Few may just have skin or eye lesions and which usually follow PROM.<sup>44</sup>

## Perinatal HSV Infection

Babies may present up to 5 days of life with no defining symptoms. Between 5 and 21 days of life,<sup>43</sup> presenting symptoms include fever, lethargy with seizures and respiratory distress. Typical vesicular rash may only be present in 40% and many infants never show any presence of vesicles.<sup>45</sup> Higher mortality rates are seen in the premature, those with disseminated intravascular coagulation, seizures, and/or altered conscious state.<sup>44</sup>

Cutaneous involvement is seen as discreet, as well as clusters of vesicles, that usually erupt on an erythematous base and are 1–2 mm in size. These vesicles may progress to larger bullous lesions. Infections involving the eye may manifest as keratoconjunctivitis or later as chorioretinitis.

Differential diagnoses include varicella zoster, enterovirus disease, and disseminated CMV disease. Vesicular lesions can imitate those caused by *Listeria monocytogenes* and so can those caused by bullous impetigo, enteroviruses, and CMV. Consideration should also be given for toxoplasmosis, rubella, and syphilis.

Mortality rates are dependent on whether the disease is involving the skin and mucous membranes or the CNS or it is disseminated. Treated skin and mucous membrane disease may have no mortality and a normal outcome in 98%, whereas disseminated disease may have a mortality of 30% even with treatment.<sup>40,46</sup>

Disseminated disease occurs in 25% and CNS disease in the form of encephalitis may occur in up to a third of neonates. It seems that maternal placental antibodies may prevent disseminated disease but not the spread of virus to the brain.<sup>47</sup> CNS involvement may present at 10 days up to 4 weeks of age with fever, lethargy, and irritability, seizures, focal neurological signs, and a bulging fontanelle. CSF shows predominantly mononuclear cells and elevated proteins. Untreated the mortality rate may be 50% and



morbidity, despite high dose of acyclovir and particularly, with neurological complication is common.

Even those infants presenting with skin and mucous membrane disease may progress to dissemination and in one study 24% had HSV DNA in the CSF detected by PCR testing.<sup>48</sup> Bullous lesions may recur as they follow viremia, which can be reactivated later in infancy. If there are more than three recurrences in the first 6 months of life, poor neurological outcome may occur.<sup>49</sup>

## Management of Neonatal HSV Infection

Early institution of therapy with a high index of suspicion is essential as only 40% will have bullous lesions and the mother may have been asymptomatic.<sup>45</sup> Progressive abnormalities of liver function may occur along with hepatosplenomegaly and thrombocytopenia. After consideration of the diagnosis antiviral therapy should be given immediately.

## Diagnosis

Rapid and very sensitive and specific PCR testing of lesions as well as viral culture of the CSF may be diagnostic.<sup>48</sup> Also culture specimens are suitable from blood, throat, nasopharynx, conjunctivae, and rectum or urine.

## Treatment

Intravenous acyclovir 20 mg/kg every 8 hours<sup>49</sup> is given for 21 days in cases of disseminated infection.<sup>15</sup> Long-term suppressive treatment to prevent cutaneous recurrence (commonly HSV2) and CNS complications need further study before routine recommendations can be made.<sup>50</sup>

## HUMAN PAPILLOMA VIRUS (HPV)

Human papilloma virus genital types can be transmitted to the baby, mostly at birth through an infected birth canal. Maternal genital warts (usually non-oncogenic types 6 and 11) can increase in size and number during pregnancy and may be transmitted to the neonate. The vast majority of genital warts in pregnant women clear up post delivery.

HPV types 6 and 11 have been associated with laryngeal papillomatosis in children but this usually presents after 3 up to 4 years.<sup>51</sup> The incidence given is one case/3.5 million person-years and a prevalence of four cases per 100,000 children.<sup>52</sup> This serious complication particularly when recurrent is rare. HPV colonization in the neonate is transient in most cases.

Although HPV DNA has been found in amniotic fluid and in cord blood samples,<sup>52</sup> it is still unclear whether this route of transmission is significant. Jayasinghe has reported in a study of 574 women that 1.65% of newborns were HPV DNA positive at a mean of 65 hours after birth.<sup>53</sup> However, from the studies done it is clear that contamination rather than infection had occurred in most cases and even HPV 16 antibodies clear by 10 months.<sup>54</sup> Caesarean section is not indicated to prevent transmission of

HPV although occasionally genital warts may be so large vaginally as to be a risk of obstructive labor and recourse to caesarean delivery is thought necessary.<sup>55</sup>

## NEONATAL HEPATITIS

Neonatal hepatitis can be caused by Hepatitis B and C as well as other STIs particularly syphilis and CMV.

## Neonatal Hepatitis B

Most of HBV transmission occurs from asymptomatic carriers during labor and delivery. Although the exact mechanism is not known, it is presumed to result from exposure to maternal blood, genital secretions or both. Transmission is more common from women with the presence of HBeAg in their blood.

Twenty five percent of women with acute Hepatitis B during pregnancy may have a premature delivery, less commonly, an abortion or a still birth. The child may also present with failure to thrive, jaundice, and could proceed to liver failure if the mother has had acute Hepatitis B pre-delivery. If acute infection occurred in the last trimesters there is 70% risk of transmission to the baby. If acute Hepatitis B occurs in the first two trimester there is a 5% risk. If the mother is HBeAg positive the risk of infection from the mother to the child is up to 90% during delivery. If the mother has got HBcAb and is negative for HBeAg, the risk is much lower. Unfortunately, if infected the child is often asymptomatic and may develop chronic carriage in 90% of cases compared to adults, where only up to 10% of those infected, may go on to persistent carriage.

Perinatal transmission is the usual method of acquisition and policies of prevention of infection from mother to child have been in place for some years and have been assessed regarding efficacy. A 10 year neonatal Hepatitis B vaccination program in the Netherlands from 1982 to 1992 documented 705 infants from Hepatitis B antigen-positive mothers. Eight infants were born to 114 HBeAg positive mothers and became carriers within the first year of life with the protective efficacy rate (PER) of passive and active immunization at 12 months follow-up at 92%. The factor affecting the PER was the level of maternal HBV DNA. PER was 100% if maternal HBV DNA was less than 150 pg/ml and 68% for HBV DNA levels more than 150 pg/ml.<sup>56</sup> At 5 years follow-up significantly more infants had loss of sero protection who started active immunization at birth as compared to those starting at age of 3 months.

The clinical manifestations were reported in a study of mothers with acute Hepatitis B where HBsAg was detected in 17 out of 31 infants. Neonatal infection developed in one of 10 babies when maternal hepatitis occurred in the first two trimesters and in 16 of 21 babies when it occurred in the third trimester or within 2 months after delivery. Two of the 17 infected infants developed jaundice at 3 and 4 months of age and 13 infants who became infected showed no clinical signs of illness although they retained their antigen positivity for up to 39 months with raised liver enzymes (SGPT). Also liver biopsies on 10 infants between 3 and 27 months of age showed features of unresolved hepatitis.<sup>57</sup>

Prevention protocols for neonates usually consist of giving Hepatitis B immunoglobulin (HBIG) one dose of 0.5 ml intramuscularly within 12 hours of birth. At the same time, Hepatitis B vaccination is delivered in a different site intramuscularly and repeated at 1–2 months and at 6 months.

Hepatitis B can possibly be transmitted to breastfed infants from mothers who are chronic Hepatitis B carriers. However, in a study from Texas where HBV carriers were given HBV immunoprophylaxis and followed up for 15 months, none of 101 breastfed (mean length of breast feeding 4–9 months) infants but nine of the formula fed infants (3%) were positive for HBsAg.<sup>58</sup> It can be inferred that with appropriate immunoprophylaxis, breast feeding of infants by chronic HBV carriers poses no additional risk of transmission.

## Hepatitis C

Kumar et al. studied 830 pregnant women in an Indian antenatal clinic with testing for anti HCV with a third generation ELISA. Antibody-positive women were tested for HCV RNA and the mothers were evaluated for the presence of risk factors for HCV infection. 1.03% (84) women had HCV antibodies and 46 of these (54.8%) were positive for HCV RNA. There were no recorded risk factors for HCV positive status.<sup>59</sup> This infection varies in prevalence in different populations and in countries and in women with different risk factors, i.e. rates may be higher in IV drug using women.

Thomas et al. reviewed 976 infants from 28 studies followed up sufficiently for recalculation of transmission rates. Overall transmission rates were less than 10% in 8/12 studies of HIV-negative mothers, compared with 2/7 studies comprising at least 50% HIV-coinfected mothers. Nine studies measured maternal viremia levels, with only 2/30 transmitting mothers having <10(6) copies/ml of HCV RNA. Eight transmissions were identified overall from non-viremic mothers.<sup>60</sup> Majority of infections are probably acquired from infectious blood at delivery although the infant may not be viremic until several weeks afterwards. Current opinion does not support the use of caesarean section to prevent transmission.<sup>60,61</sup>

Antibody to HCV will be present in the infant at delivery which can be maternal. There is no indication for testing cord blood. Confirmation of infection should be done at 4–6 months by HCV RNA (HCV PCR) as well as liver function tests. Transplacental antibody can be present for more than 12 months but if there is positive HCV RNA, pediatric referral is indicated.<sup>62</sup> In the Hepatitis C/HIV co-infected mother, after the first trimester, antiretrovirals should be prescribed to reduce the transmission of both HIV and HCV. PROM is a risk for HCV transmission and the use of scalp electrodes or amniocentesis should be avoided. Unfortunately, unlike Hepatitis B there are no interventions that can limit perinatal transmission.<sup>63,64</sup>

Although Hepatitis C can be transmitted perinatally and is present in the breast milk, actual infection following transmission through breast milk has not been described.

## Hepatitis G (GB Virus Type C)

Mother to infant transmission of hepatitis G virus has been documented. In a study of 2046 women predelivery, 46 mothers (2.1%) were positive for hepatitis G RNA and 25 of their infants were followed up for 12 months. Thirteen infants (52%) were viremic and this continued to persist. In the 12 uninfected infants, the mothers had lower viral load copies per ml at the time of labor, inferring that high-titer maternal viremia and mode of delivery are closely associated with mother-to-infant transmission (two high-titer mothers had elective caesarean sections).<sup>65</sup>

Maternal-to-infant transmission of hepatitis G may occur in 75–80% of cases while the rate of HCV is much lower at 2.8–4.2%.<sup>66–68</sup> HGV does not seem to induce hepatitis in the children.<sup>68</sup>

## CYTOMEGALOVIRUS INFECTION (CMV)

Cytomegalovirus can be transmitted to the neonate *in utero* (up to 2.4%). Ten percent of these congenitally infected children may have symptomatic disease at delivery. Cytomegalic inclusion disease (CID) may follow primary infection of women usually during the first half of pregnancy. During delivery, 2–28% of positive mothers may be shedders from the cervix and 50% of the infants may be affected. Because of maternal antibodies, the infant may rarely have symptomatic disease.

Reactivation of CMV in breast milk is very common if milk whey is analyzed by PCR.<sup>69</sup> Ninety six percent of seropositive mothers in this study had viral DNA in breast milk at a median of 3.5 days postpartum and infectious virus at 10 days. The majority of infected infants are asymptomatic and this is possibly related to maternal antibody, but there is a risk of disease particularly pneumonia in preterm infants or infants treated with steroids. In this study, congenital disease was ruled out with 87% of deliveries by caesarean and negative PCR taken at birth. Pasteurization of breast milk may inactivate CMV.<sup>70</sup>

CMV can be transmitted to the neonate by transfusion of non-screened blood.<sup>71</sup> In most neonates, symptomatic disease occurs if the mother was seronegative. The incidence is 10–30%, particularly in preterm infants and it has been shown previously to be related to the number of donors and titer of CMV in donor blood.<sup>70</sup> Prognostic outcome may be related to neonatal blood viral loads.

## Asymptomatic Infection

Almost 90% of infants with congenital CMV infections are asymptomatic and their long-term outcome is good. However, 5–15% of them are at risk of developing developmental abnormalities including sensorineural hearing loss (CMV is the commonest cause of this acquired congenitally), microcephaly, motor deficits, mental retardation, chorioretinitis, and dental defects, which become apparent within the first 2 years of life.

## Symptomatic Infection

The incubation period varies from 4–12 weeks. A febrile pneumonitis can occur as well as hepatosplenomegaly,

neutropenia, lymphocytosis, and thrombocytopenia. At birth neurological involvement can be diagnosed by PCR testing of the CSF. Even with asymptomatic disease a positive result correlates with poor neurodevelopmental outcome.<sup>72</sup>

CMV can be transmitted from person to person through body fluids and can be found in blood, urine, semen, cervical secretions, saliva, breast milk and transplanted organs and as with all herpes viruses affecting mucous membranes it can be intermittently excreted.<sup>73</sup> Viruria ensures isolation/PCR positivity from urine. Saliva, white blood cells, CSF, stool, and biopsy specimens can be positive for the virus. Amniocentesis is valuable antenatally for diagnosing CMV using viral culture and PCR tests.

In a study to assess maternal risk factors in 175 mothers against controls, women with gonorrhoea, trichomoniasis or BV had an increased risk of intrauterine transmission of the CMV as did those who were primigravid. The risk was also increased in young unmarried and lower income mothers studied in a predominantly black, low-income population.<sup>74</sup>

## Treatment

Ganciclovir 8–12 mg/kg given in divided doses at 12 hourly intervals for 6 weeks has been used with variable effects as assessed at 6 months or more. Oral Valganciclovir given as a dose of 16 mg/kg provides similar efficacy. Both these drugs can lead to neutropenia in 38% of patients.<sup>70</sup> In Iran, prolonged courses of oral analogs of ganciclovir for children with symptomatic congenital CMV are offered.<sup>75</sup>

## Conclusion

Neonatal STIs can have severe acute and long-term complications. Their recognition requires a high index of suspicion and early diagnosis and treatment is essential. Their epidemiology reflects that of the local adult population. Preventive measures should therefore be primarily directed at limitation of adult STIs through education, readily accessible and acceptable sexual health services, maternal screening, and use of barrier contraceptive techniques in high-risk populations.

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## Introduction

*“The child enters the world with an enormous syphilitic burden ... (it) is a saturated solution of syphilis ... organs and tissue ... are swarming with treponemata.”*<sup>1</sup>

Congenital (also called intrauterine or antenatal) syphilis (CS) occurs when a fetus is infected with *T. pallidum* while in utero and is currently a growing case of concern for public health, especially in the third world, with 3–15% of women in their reproductive years infected and places where up to 17% of pregnant women have a positive serology.<sup>2,3</sup> In spite of the shortage of formal or complete records, statistics by the WHO allow an estimation of a million pregnancies negatively affected by syphilis each year.<sup>3–5</sup> CS in sub-Saharan Africa accounts for 11% of the 4 million neonatal deaths worldwide.<sup>6,3</sup> Where syphilis is prevalent, it may cause up to half of all stillbirths.<sup>7</sup>

The typical victims are fetuses from young mothers without adequate antenatal care (or none at all). They will become infected up to 95% of the times because the treponemes will reach them transplacentally via the blood. This transfusion of infected blood from the mother results in secondary syphilis in the fetus.<sup>8</sup> Besides abortion, stillbirth, and perinatal death, syphilis in the mother can lead to newborns with hepatosplenomegaly or babies born with early or late stages of syphilis, which in two thirds of the cases may be asymptomatic at birth and develop later causing characteristic malformations in the teeth and skeleton.

## History

Sexually transmitted infections (STIs) have had a significant impact on individual and collective lives within society since early history. Such is the case of syphilis, which has caused real epidemics affecting large numbers of people in Europe, the Middle East, and in America with devastating consequences throughout history. In spite of the controversies surrounding the origin of syphilis, it was undoubtedly recognized in Europe by the end of the fifteenth century and it became a fast-growing multinational epidemic, where the sexual aspect was predominant and its clinical traits made it be known and feared.<sup>9</sup>

Syphilis in infants has been described since the late fifteenth century, almost in parallel to the great European pandemic, and was the only non-venereal form of transmission found in medical descriptions once the most virulent phase of the disease had passed.<sup>10</sup>

In 1529, a hereditary component was described by Paracelsus, who believed the contagion was transmitted from father to child during conception.<sup>11–13</sup> Niccolò Massa, in 1537, concluded that children who were infected but had not been breastfed had received the disease through their mother's infected blood.<sup>14</sup> Still in the sixteenth century, French physician A Ferrier saw infection during conception or through “vicious humors” from the pregnant mother.<sup>12,15</sup> Later, in the seventeenth century, the high rate of miscarriages, stillborns, and infant death was attributed to “plague, smallpox, and venereal disease,”<sup>16</sup> and by the end of the eighteenth century, in L'Hôpital des Vénériennes, in Paris, anti-syphilitic treatment was given to mothers, their newborns, and their nurses.<sup>17</sup>

The knowledge about syphilis in all its forms gained momentum after the 1850s, a time rich in discoveries on different fields in the natural sciences. The development of the ideas from the nineteenth century that affected the concepts about CS is outlined below. In the history of venereal disease, morality plays a very important part, since the great majority of the afflicted had acquired it through sin; i.e., illicit sexual activity. The origin of every infection could be traced back to prostitution and their promiscuity.<sup>18</sup> But in the case of CS, innocent babies were suffering (*“the monster is seen in its most cruel form where the innocent baby is its victim”*<sup>19</sup>). CS appears in plays and literature from the end of the nineteenth century and beginning of the twentieth. Famous cases are H Ibsen's play *Ghosts* (1881), the short story by Sir AC Doyle, *The Third Generation* (1894), and E Brieux's *Les Avariés*—named *Damaged Goods*, in English (1901). Ibsen's play is about the wife of an adulterous man who discovers that her son has CS; Doyle's story has an innocent young man committing suicide after finding out that he is infected because of the loose ways of his grandfather (assuming Lamarckian transmission that did not involve the mother) and therefore

should not marry. In *Les Avariés*, a less honorable man hides his disease from his bride and she gives birth to a syphilitic child. This play was called “*a powerful plea for light on this hidden danger that fathers and mothers, young men and young women, may know the terrible price that must be paid, not only by the generation that violates the law, but by the generations to come.*”<sup>20</sup>

Treponemes remained elusive until the twentieth century. Discovered in 1905 by zoologist Fritz Schaudinn and dermatologist Eric Hoffmann,<sup>21,22</sup> they were stained in 1906 with silver nitrate and demonstrated in tissues from infected newborns by C Levaditi.<sup>23</sup> Shortly afterwards, on the same year, AP von Wassermann, ALS Neisser, and C Bruck developed what became known as the Wassermann reaction, using treponemal antigens extracted initially from the liver of a dead syphilitic baby.<sup>21,24,25</sup> It was later shown that the test did not detect treponemes but the damage caused by them.<sup>25</sup> Nonetheless, it was fundamental to diagnose the presence of the pathogen and thus remission from the disease during or after treatment.<sup>21</sup>

## Changing Concepts about the Causes and Nature of Infantile Syphilis

Using the terminology of the nineteenth century, syphilis in the newborn could be “primitive,” if acquired from a lesion in the mother during birth or shortly after, and “hereditary,” if a parent (almost always the father<sup>26</sup>) was “tainted” with an active or latent syphilis during conception,<sup>27,28</sup> or if the pregnant mother passed it to the fetus through the blood.<sup>29,30</sup> For some, only the latter was considered “congenital,”<sup>31</sup> but for others, the father’s seed, the mother’s blood, and the nurse’s milk could all transmit “hereditary” syphilis.<sup>32</sup>

### TRANSMISSION THROUGH MILK

In 1499, G Torella noticed that infants would be infected by their nurses through their milk or lesions in the breasts or mouth.<sup>11,33</sup> A Paré, in the sixteenth century, tells about a wet nurse who was sent to prison to be lashed as a punishment for infecting a whole family with syphilis.<sup>34</sup> Much later, looking at the case, it could be hypothesized that the nurse was in fact a victim of the disease of the father of the family, whose child had CS and transmitted it to her when breastfeeding. These cases of acquired syphilis, abundant in the literature of the eighteenth and nineteenth centuries,<sup>35,27</sup> can be summarized by the words of a physician called B Mandeville in 1724: “Men give it to their wives, women to their husbands, or *perhaps* their children; they to their nurses, and the nurses again to other children...”<sup>29,33</sup> There were no doubts about children transmitting primary syphilis,<sup>11</sup> and to prevent wet nurses from being infected, artificial nipples of different materials (wood and cork or even silver) were used.<sup>36</sup> In fact, children from syphilitic parents were not supposed to be breastfed by a healthy nurse; the general recommendation since the second half of the nineteenth century was for the mother to feed the baby, because her latent syphilis conferred immunity.<sup>27,37</sup>

In the eighteenth century, the quality of breast milk was recognized as paramount for the child’s development, and if a

wet nurse had to be used, she was to be carefully selected—even her character, emotions, and mood would greatly affect the health of the child.<sup>38</sup> Again, moral played an important part because, mostly, wet nurses were women of low resources and very possibly “unclean,” with illegitimate children. If syphilis could actually be transmitted through milk was still debatable in the nineteenth century; some physicians were uncertain and expected further corroboration,<sup>11,39,40</sup> some considered the possibility,<sup>32,41</sup> while others focused in the arguments against it, which outweighed those in favor: no one could show evidence of an alteration of the milk due to disease and since it didn’t have “cellular elements,” it was incapable of carrying the poison.<sup>15,42</sup>

### INHERITANCE OF INFECTION

Already in 1558, Paracelsus wrote that the French plague was hereditary.<sup>12,15</sup> Two hundred years later, in pre-revolutionary France, CA Vandermonde advised great care when choosing one’s partner; looking for natural beauty and avoiding “weak” individuals would prevent the inheritance of acquired diseases like syphilis and scurvy. For him and others, who advocated “physical and moral hygiene,” decadent behavior had brought infant mortality and infertility.<sup>43</sup>

In his influential *Treatise on the Venereal Disease* (1786),<sup>42</sup> John Hunter had denied the possibility of hereditary syphilis; he thought that only primary syphilis was contagious, wrongly dominating the ideas about the transmission of the disease for a long time. But in the following century, frequent discussions arose among experts from different medical fields, with opposing or complementary points of view about the causes and different aspects particular to infantile syphilis.<sup>15</sup> There was just too much conflicting evidence and too many interrogants.

Mothers who were apparently healthy alternated stillbirths with diseased and healthy newborns, and women who were patently syphilitic could give birth to healthy children. Sometimes twins would manifest the disease (or not) in completely different ways.<sup>11,29</sup> These observations meant years of confusion as to the route of transmission. Scientific journals from the nineteenth century abound in reports by perplexed, caring physicians describing healthy (“*plump, handsome and interesting*”) women falling ill shortly after marrying men who had been treated years before and had no longer symptoms. The Medical Times and Gazette of London stated: “*The father has the most direct influence over both mother and child’s health and can be called the origin of infection; diseasing a woman and the offspring is sure sign of latent syphilis.*”<sup>31</sup>

Thus, if the father had syphilis during conception, his sperm introduced the poison and, by dividing in the womb, gave it to every single tissue of the fetus,<sup>44</sup> killing it sooner or later “*...the fecundated germ... is blighted from the first.*”<sup>45</sup>

If the father was already cured, he was not contagious; the mother became poisoned only through the poisoned blood of the fetus, in contact with the placental blood.<sup>11,45–47</sup> Virtuous,



innocent mothers were thus infected by their syphilitic fetuses, while unmarried women with “loose habits” were always seen as the sources of contagion. Innocent or not, if the mother was infected, the main mode of transmission of CS was undoubtedly through the blood. In any case, the disease was the same, coming from the mother or the father.<sup>26</sup> Trying to understand the nature of transmission, physicians carefully registered each case adding information about the source of the disease: “father alone, mother alone, both parents”.<sup>48</sup> To collect this kind of information was hard for general practitioners, since the usual way for them to find out that a pregnancy was endangered was to notice a pregnancy in the mother who took a syphilitic infant or child to the hospital; only through careful questioning a previous history of miscarriages and a possibly latent infection in the father would be known. One of the first such studies was by M. Kassowitz, who in 1875 presented statistics from 330 children (or fetuses) belonging to 119 family histories obtained after years of observation and careful notes.<sup>15</sup> Another study on families showed 66% of mortality and a majority of weak, stunted, infantile syphilitics among the survivors.<sup>49</sup>

## INFLUENCE OF PARENTS

In the second half of the nineteenth century, embryology was becoming a modern science, based on cytology. K von Bauer had discovered the mammalian ovum in 1827, but although the cell theory was also being born, it took almost thirty years for both it and the spermatozoon to have the status of “cells.”<sup>50</sup> In 1875, after decades of debate on the influence of male and female on conception, O Hertwig established that fertilization involved the conjugation of both parts in a single cell.<sup>51,52</sup> It was therefore proposed that transmission of the syphilitic poison to an unborn child could come from two sides: during conception, from the mother’s ovum or the father’s sperm cell, both equally capable of transmitting characteristics (proper inheritance), or by transplacental infection in utero, with the mother as sole agent.<sup>12,15</sup> It had been proposed that syphilis from the father affected mainly the fetus’ liver, and that from the mother, its lungs.<sup>15</sup>

As for the effects of infection of the mother over the development of the fetus, in 1853 P Ricord took Hunter’s *Treatise* and added a new section on infantile syphilis stressing that “*an infant is badly lodged and poorly nourished in the womb of an infected mother, apart from the influence of the virus.*”<sup>42</sup> Abortion, miscarriage or stillbirth could happen even if the fetus was not syphilitic, only due to the defective nutrition from a sick mother.<sup>15</sup>

The effects of syphilis had been carefully studied by the late nineteenth century and some laws formulated concerning pregnancy: 1) syphilis before conception is more prone to abortion than if acquired during pregnancy; 2) if contagion happens at the time of conception, the rule are abortion and stillbirth; 3) if the disease is acquired in late pregnancy, the chances of survival are much better.<sup>45</sup>

## A “SYPHILITIC YEAST”

An interesting debate among the members of the Pathological Society of London took place in several sessions from February to April of 1876, starting and concluding with lectures by J Hutchinson. Talks of a living form capable of multiplying and developing in blood and tissues, a “syphilitic yeast”, were without any doubt inspired by L Pasteur’s works on fermentation, which favored the germ theory of disease against that of spontaneous generation.<sup>53</sup>

G Mendel’s Laws of Heredity had been published in 1865, but remained obscure until 1902.<sup>54</sup> Their recognition, together with the identification of the etiologic agent of the disease and the means to demonstrate its presence, finally invalidated both the concept of hereditary transmission (“*a micro-organism can never be part of inheritance*”<sup>1</sup>), and that either parent could be the direct source of infection. After 1912, the term “hereditary” was dropped from the medical literature about syphilis, remaining only “congenital” and “infantile syphilis.”

## History of Prevention and Antenatal Treatment

The Vaugirard hospice, opened in 1780 in Paris and devoted to children affected by venereal disease, allowed for the closer observation of a larger number of cases.<sup>55</sup> The sight of those children who survived was pitiful, and their short lives served as a punishment for the sins of their parents and as warning against libertine ways. The risk of a weak generation was also evident if diseased persons were to procreate.<sup>33</sup>

A charity institution to treat venereal disease opened in 1747 in London, the Lock Hospital. Trying to change the concept of sinful women as bearers of evil, the benefactors beheld them as victims and acknowledged that many of them had been infected by vicious husbands, diseased parents or children who were perhaps not theirs and had contracted the disease from a nurse. Progressively, married women and their children were treated as innocent while others were clearly considered guilty of their misfortune.<sup>56</sup>

In 1852, syphilization as a preventive or curative therapy was officially condemned by the Paris Academy of Medicine after a report that considered it “monstrously unreasonable,”<sup>57</sup> but in 1856, Norwegian CW Boeck reported using it on infants with CS in Christiania (now Oslo); he later wrote “my experience of the treatment of hereditary syphilis justifies me in continuing to practice syphilization...”<sup>58</sup>

Preventive medicine, as early as possible, was proposed: a positive Wassermann reaction in a mother or her newborn (even if apparently healthy) would indicate the need for treatment; children from parents shown to be free of the infection for over two years would be tested periodically during the first 2 years of life.<sup>1</sup>

Proper and early treatment would even alleviate society from potential criminals, since their “extremely unstable nervous equilibrium” made congenital syphilitics more prone to be delinquent.<sup>1</sup> The availability and efficacy of treatment (Salvarsan)

made it evident that early diagnosis and proper surveillance of the pregnancy could prevent CS.

The spread of antenatal care to the general population as well as pathological research on expelled, “macerated” fetuses, in the look out for *Spirochaeta pallida*, was strongly advocated by practitioners before the 1920s,<sup>49,59</sup> when Dame Janet Campbell in the UK started a national system with regular visits and procedures.<sup>60</sup> In 1923, an editorial in *Nature* citing a report of the Committee of Inquiry on Venereal Disease, by the Ministry of Health, read: “*It seems within the bounds of possibility that inherited syphilis may cease to exist some day, so effective is the treatment of the syphilitic mother during pregnancy in securing a healthy baby...*” The author was referring to treatments that combined mercury and salvarsan.<sup>61</sup>

Penicillin was found to be effective in 1943; in spite of the idea that it could be abortive,<sup>62</sup> it was used in pregnant women and first reports of encouraging treatment of CS were also discussed in *Nature*.<sup>63</sup> It prevented transmission to the fetus and could also cure it. Moreover, relatively small doses were effective treating infants with CS.<sup>64,65</sup> Sure enough, besides providing treatment, combating promiscuity was also a public health measure needed for the prevention of CS.<sup>66</sup> Antenatal care and treatment to prevent as many children as possible from being born as “such ghastly incarnations of hopeless misery”<sup>49</sup> means also less fatalities among the unborn<sup>45,59</sup> and with it, much pain within families.<sup>16</sup> Somehow shockingly, these losses could be openly disregarded: “*If every product of conception of a syphilitic mother were to reach maturity, the world would much sooner become over-populated and unable to support its inhabitants than would otherwise be the case. From this point of view alone I would not strongly advocate the antenatal treatment of syphilis, but from the point of view of preventing the unnecessary suffering of congenitally syphilitic children, the unhappiness it causes to the parents of such children. I most emphatically recommend the treatment of the pregnant syphilitic mother, for the sake of her child and of her own future health.*”<sup>7</sup>

Altogether, the twentieth century brought development and improvements that were reflected in a wider use of antenatal care in the whole world.<sup>67</sup> For the twenty-first century, the prevention of mother-to-child transmission of syphilis through more access to maternal health services, and an established surveillance of pregnancies including new technologies as point-of-care diagnostics was set to achieve the goal of eliminating CS as a public health problem.<sup>68</sup>

## Epidemiology and Burden of Disease

In the public health arena, syphilis shows its most negative effect when observed from the maternal and child health side. In 1948, the United Nations signed the Universal Declaration of Human Rights committing all the signatory members to particularly protect the health of the mother and child (United Nations, 1948). More than 60 years have gone by and the progress in protecting the mother-child health has been irregular. Interventions aimed at improving food, immunization, and integral management of diseases have had

measurable and beneficial effects and have achieved improvements in child survival. However, in spite of the significant decrease in mortality of infants and children under 5 years of age, there are still countries where mortality of these groups remains high, particularly in the developing part of the world.

The World Health Organization (WHO) estimates 3.3 million stillborn and over 4 million children who die before reaching 28 days of life.<sup>67</sup> According to WHO, the main causes of mortality in children under five lie on neonatal-stage pathologies with neonatal infections and prematurity as the most frequent causes.<sup>67</sup> WHO also estimates around 2.1 million pregnant women with active syphilis per year. Syphilis might be responsible for at least 500,000 perinatal deaths per year in Sub-Saharan Africa alone.<sup>69</sup> CS represents an important cause of mortality in this age group and some reports state that it may be the cause of as high as 26% stillborns.<sup>70</sup>

## CASE DEFINITION FOR CONGENITAL SYPHILIS

The case definition of CS changed from the classic criteria established by Kauffman<sup>71</sup> to that suggested by the Centers for Disease Control (CDC) in 1989. The CDC criteria includes newborns with clinical evidence of active syphilis, as well as those who do not present any signs, but whose mother suffered from an untreated or inadequately treated syphilis (CDC, 1989).<sup>72</sup> Table 92.1 shows some differences between the Kauffman and the CDC criteria for the case definition of CS.

The use of the CDC criteria increased the sensitivity of CS case reports, although high-risk cases that may not be infected were also included. The effects of the change of the criteria on the surveillance of the incidence of CS may be observed in the

**Table 92.1:** Differences Between the Kauffman and the CDC Criteria for the Case Definition of Congenital Syphilis

Kauffman criteria	CDC criteria
<b>Definite</b> Detection of <i>T. pallidum</i> in dark field or histological samples	<b>Confirmed</b> Laboratory demonstration of <i>T. pallidum</i>
<b>Probable</b> Increase in VDRL titers over 3 months or serological test that do not seroconvert after 4 months One major criterium or two minor ones plus a positive syphilis serological test or FTA One major and one minor criteria	<b>Presumptive</b> Any child of a mother with untreated or inadequately treated syphilis Any child with a positive serological test plus: Clinical findings compatible with syphilis VDRL in CSF or CSF with >5 cells or >50 mg/dl proteins with no other cause Reactive IG test for syphilis
<b>*Possible</b> FTA reactive test without clinical signs	<b>Syphilitic stillborn</b> Fetal death of over 20 weeks or 500 g weight to a mother with untreated or inadequately treated syphilis

Major criteria: condyloma lata, osteochondritis, periostitis, and hemorrhagic rhinitis. Minor criteria: scars in the labia, mucocutaneous lesions, hepatomegaly, splenomegaly, lymphadenopathy, hemolytic anemia, and neurological signs.

statistics of countries, as happened in the United States, where an important increase in the number of cases was seen after the change in case definition criteria for CS.<sup>73</sup>

### CONGENITAL SYPHILIS ESTIMATES

The rate of CS is directly related to the rate of syphilis in women at a reproductive age. Seroprevalence during pregnancy is quite low in the developed world, ranging from 0.002 in Europe to 4.3 in some regions in the United States.<sup>74</sup> However, few of these infections lead to CS due to very efficient prenatal care. For instance, in the United States, 13.4 syphilis cases per 100,000 live newborn were reported in 2000,<sup>74</sup> whereas nine presumptive cases of CS were reported in the United Kingdom between 1994 and 1997.<sup>75</sup> In contrast, CS case rates dramatically increased in rural areas of Eastern Europe and Asia.<sup>76</sup> In Africa, a high prevalence of maternal syphilis is reported in a sustained manner (3–18%) in prenatal clinics and because of this, CS rates are higher than 1% in day care centers.<sup>77</sup>

In the Latin American and Caribbean region in 2004, according to the Pan-American Health Organization (PAHO), the national STI/HIV/AIDS programs reported estimated prevalence rates of 3.1% in pregnant women with syphilis in the region, ranging from 1.00% in Peru and 6.21% in Paraguay. According to these data, the incidence of CS ranges from 1.40/1000 live births in El Salvador to 12/1000 live births in Honduras, whereas in the United States it is 0.10 cases per 1000 live births.<sup>78</sup> A recent survey,<sup>79</sup> which included 19 Latin American states showed that the commitment to eliminate CS has been taken up by all the countries, but at least 12 out of the 19 have not reached the minimum acceptable figure proposed as a target by PAHO: 0.5/1000 live births. (Fig. 92.1) Bolivia, Paraguay, and Haiti are the countries

that must make a greater effort to reach the proposed goal. Some of these countries do not consider the reporting of CS to be compulsory, although this is absolutely essential if the elimination program is to make progress.<sup>80</sup>

Schmid using data from the literature has estimated annually around 2 million maternal syphilis cases and from 728,547 to 1,527,560 congenital syphilis cases in the world<sup>81</sup> (Table 92.2).

The World Health Organization (WHO) estimates that each year, maternal syphilis is responsible for 460,000 abortions or stillbirths, 270,000 congenital syphilis cases and the birth of 270,000 premature or low-weight babies.<sup>82</sup> Adverse results in pregnancy are 12 times higher in women with syphilis than in seronegative women.<sup>83</sup>

A recent systematic review including 10 studies of interventions to improve the outcomes of antenatal syphilis screening has shown that it could reduce the syphilis-attributable incidence of still birth and perinatal death by 50%.<sup>84</sup>

Several studies mention the frequency of adverse events in untreated maternal syphilis. Some of them are summarized in the Table 92.3. The fact is that these adverse events average 65% of the products of mothers with syphilis, which represent a substantial negative impact of maternal syphilis in perinatal morbidity.

The prevention of congenital syphilis is based on syphilis screening in pregnant women and timely treatment with penicillin of those who are infected. Penicillin is highly effective, safe and the only recommended treatment for all pregnant women with syphilis.<sup>85</sup>

**Table 92.2:** Global Estimates of Syphilis in Women and Adverse Pregnancy Outcome due to Syphilis

Proportion of seropositive women with:	Conservative model (Watson-Jones et al.)*	Mid-range model (Schulz et al.)†	Less conservative model (Global Burden of Disease, WHO, 2000)
a. Untreated syphilis	0.95 <sup>a</sup>	1.0	1.0
b. High serological titer (≥1:8)	0.73	–	–
c. Adverse pregnancy outcome due to syphilis	0.49	0.65	0.75
Global annual number of congenital syphilis cases <sup>b,c</sup>	713,600	1,365,000	1,575,000

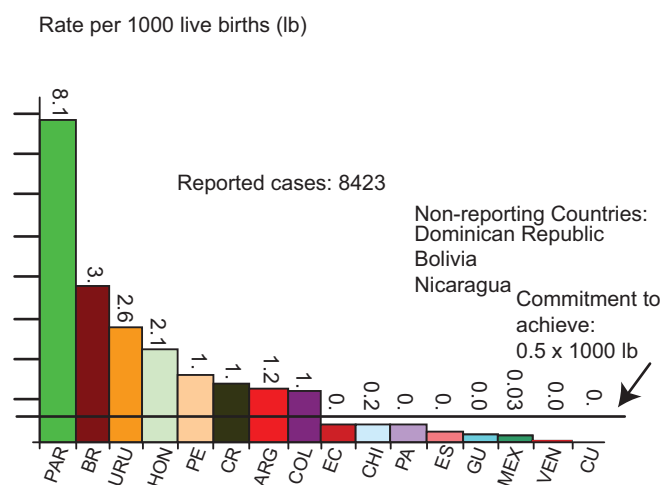
a Modified from Watson-Jones' model to reflect the proportion of seropositive women who did not receive prior treatment.

b Calculated as: 2.1 million maternal cases x Ax BxC.

c Includes miscarriage/fetal loss, perinatal death, premature birth/low birth weight, and neonatal infection.

\*Watson-Jones D, et al. *J Infect Dis* 2002;186:948–57; †Schulz KF, et al. *Genitourin Med* 1987;63:320–5.

From "The global elimination of congenital syphilis: rationale and strategy for action"—A WHO publication, 2007 (ISBN 978-92-4-159585-8).



**Fig. 92.1:** Incidence of congenital syphilis in Latin American and Caribbean Countries, 2006. PAR, Paraguay; BR, Brazil; URU, Uruguay; HON, Honduras; PE, Peru; CR, Costa Rica; ARG, Argentina; COL, Colombia; EC, Ecuador; CHI, Chile; PA, Panama; ES, El Salvador; GU, Guatemala; MEX, Mexico; VEN, Venezuela; CU, Cuba.



**Table 92.3:** Summary of Some Studies Reporting Rates of Adverse Events Associated with Maternal Syphilis\*

	1917 Harman	1951 Ingraham	1987 Schulz	1990 Hira	2000 Global Burden of STI	2000 Watson-Jones
Abortion	17%	22%	30–40%	22%	20%	25%
Stillborn	23%	12%	10–20%	No data	15%	No data
Congenital syphilis	21%	33%	10–20%	2%	20%	No data
Pre-term delivery	No data	No data	No data	33%	20%	25%
Any of the above	61%	67%	50–80%	57%	75%	49%

\*From “The global elimination of congenital syphilis: rationale and strategy for action”—A WHO publication, 2007 (ISBN 978-92-4-159585-8).

## Pathology

*Treponema pallidum* can initiate an active infection in the fetus at any time during pregnancy after breaching the protective barrier formed by the placental villi, the amniotic membrane, and the maternal mucosal surfaces, along with their secretions. In adult syphilis, lesions are characterized by a pronounced mononuclear infiltration<sup>86,87</sup> with lymphocytes, macrophages, variable numbers of plasma cells and occasional polymorphonuclear leukocytes. Studies of the cellular phenotypes of syphilitic skin lesions in non-pregnant adults report large numbers of CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes and CD14<sup>+</sup> macrophages.<sup>88,89</sup> Varying numbers of plasma cells are also identified, but B lymphocytes are rarely detected. Most of the CD4<sup>+</sup> cells present in secondary syphilitic skin lesions have histiocytic characteristics<sup>89,90</sup> whereas immunostaining for CD3 revealed that the lymphocytes were predominantly CD8<sup>+</sup> cytotoxic T cells. Van Voorhis et al.<sup>88</sup> reported a Th1-like cytokine pattern in primary and secondary lesions with activated lesional CD8<sup>+</sup> T cells.<sup>88</sup>

Overall in CS, the more severely the fetus is affected, the greater are the pathological changes in the placenta. Placental histopathology associated with CS shows non-specific changes, including villous immaturity, enlarged villi and deciduas, plasma cell infiltrates, and proliferation of perivascular fibroblasts and endothelial cells. Acute infiltrates with polymorphonuclears (PMNs), with and without necrosis, are frequent in severe infections and chorioamnionitis. Chronic mononuclear infiltrates are also described in CS.<sup>91–95</sup> Sheffield et al.<sup>96</sup> studied placental and umbilical cord histopathology in 67 cases of confirmed CS, and found that maternal syphilis induces similar histopathologic changes in placentas as seen in adult syphilis, and noted that decidual plasma cells and chronic villitis are common regardless of the severity of the infection in the fetus. This wide histopathologic spectrum may resemble the natural history of the disease and the pleomorphism of the clinical presentations of syphilis in non-pregnant adults.

A review of the pathology of the lesions associated with CS shows a clear similarity among them. Pathology studies suggest involvement of several organs, with an extensive inflammatory response. Manifestations partly reflect the immunological maturity of the fetus—an observation noted by Silverstein 48 years ago.<sup>97</sup> In general, it is only at 22 weeks that the fetus is able to consistently build an immunological response to infection.<sup>98</sup> The interleukins, interferon levels, and the tumor necrosis factor

are much lower in premature newborns than in children born to term. This is an important finding given the central role played by cytokines in the physiopathology of CS.

In the umbilical cord of infected infants, similar changes may be seen, although histologically normal umbilical cords have been described. Acute and chronic inflammation and necrosis in the umbilical artery, umbilical vein, and Wharton's jelly are described. Funisitis is now considered the histologic marker of a fetal systemic response to intrauterine infection. Changes in the umbilical cord are classified as mild funisitis, marked funisitis without necrosis, and necrotizing funisitis.<sup>99–102</sup> The presence of *T. pallidum* is strongly associated with marked inflammation and necrotizing funisitis, and necrotizing funisitis correlates with worst outcomes.<sup>92</sup> Guarner et al.<sup>97</sup> studied 66 umbilical cords from infants born to women with syphilis and found histological abnormalities in 42% (11% necrotizing funisitis, 4% marked funisitis with no necrosis, and 27% mild funisitis); 58% of the cases had normal histology.

The immunopathogenesis of CS is poorly understood, and there is a need to define the basic components of the immune response to *T. pallidum* as a first attempt to better understand the pathogenesis of this infection. Although the cellular components of infiltrates in the placenta, umbilical cord, and fetal tissues have been extensively described, detailed immunological studies of the cell phenotypes in these tissues in CS are lacking. Acute and chronic inflammation has been described in the infected fetus. The typical inflammatory response is mononuclear and consists of macrophages, plasma cells, and lymphocytes. PMNs are rarely present in large numbers, unless in response to tissue necrosis. Abscess-like necrosis can be present in a wide variety of tissues. Gummatous lesions are not frequent; however,<sup>103–105</sup> Sheffield et al. have reported that necrotizing funisitis, acute villitis, and villous enlargement are more common findings in live born infants with CS, compared to stillborn infants in whom fetal vasculopathy and erythroblastosis were more common.<sup>96</sup> CD68<sup>+</sup> macrophages with absence of CD3<sup>+</sup> lymphocytes as a constant pathologic feature in all tissues were identified in a newborn,<sup>97</sup> and in cases of chronic syphilitic villitis, macrophages and T-lymphocytes from maternal origin were the predominant inflammatory cells with higher numbers of CD8<sup>+</sup> T-lymphocytes than CD4<sup>+</sup> T-lymphocytes.<sup>101,106</sup>

Some of the pathologic changes found in different organs in fetuses infected with *T. pallidum* are described in Table 92.4.

**Table 92.4:** Common Pathological Findings by Organ in Fetuses Infected with *T. pallidum*

Organ	Characteristics
Placenta	Thinning of the placenta; villitis with endovascular and perivascular infiltration
Liver	Inflammation of the interstitial stroma and in the perivascular tissue.
Lungs	The “pneumonia alba” is the classic lesion. The lung is yellowish-white, firm and enlarged. There is an increased amount of connective tissue.
Gastrointestinal tract	Mucosal and submucosal inflammation and mononuclear infiltration
Pancreas	Perivascular inflammatory infiltrate
Kidneys	Secondary damage by immune complex storage (similar to glomerulonephritis in adults), perivascular inflammatory infiltrate involving the interstitial tissue
Central nervous system	Involvement of the meninges, with thinning of the basilar meninges and endoarteritis. Neuronal damage dependent upon the intense involvement of blood vessels
Osseous system	May present with osteochondritis, periostitis, and osteomyelitis. The basic process of bone damage is based on the failure of the cartilage to become bone. These findings may reflect non-specific trophic changes resulting more from the direct <i>T. pallidum</i> effect from the severe generalized infection. This possibility is supported by the evidence that lesions may be cured without specific treatment.

## Clinical Features

In order to gain a better understanding of the various clinical forms of CS, ranging from fetal death to absence of symptoms in neonates, one must first understand some of the factors influencing the presence or absence of clinical forms. Fetal infection is the result of hematogenous spread of treponemes from an infected mother to the fetus. This transmission may also take place upon delivery as a result of direct contact between the newborn and the infectious genital lesions of the mother. Hematogenous spread relies on the appearance of circulating treponemes in the mother's blood. High concentration of treponemes are present in the early stages of syphilis, thus the probability of infection to the fetus in early stage maternal syphilis is close to 100%. After secondary syphilis, the probability of treponemes in blood decreases with time, thus reducing the possibility of transmission to the child when the mother's disease is in these stages.<sup>107</sup> Although the probability of transmission to the fetus may be as high as 70%, 4 years after the mother contracted the disease,<sup>108</sup> most neonates born to mothers with late stage latent syphilis are not infected.<sup>109</sup> The main factors that determine the probability of fetal transmission are the disease stage of the mother and the duration of the exposure in uterus.

In the past it was believed that the *T. pallidum* could not penetrate the placenta until after the 20th week of pregnancy. Investigators believed that the Langhan cell layer of the cytotrophoblast was an efficient placental barrier against infection during the first weeks. This theory, however, was discontinued once it was found that the Langhan cells layer was present throughout the pregnancy<sup>110</sup> and was found in women who transmitted the infection to their fetuses. Additionally, in 1974, Harter Benirschke tested fetal tissue from spontaneous abortions of women with syphilis, identifying treponemes in abortions after 9 and 10 week pregnancies.<sup>111</sup> On the other hand, Nathan et al.,<sup>112</sup> performed amniocentesis in 11 pregnant women with untreated syphilis between weeks 15 and 19 of their pregnancies (median 16.8 weeks). They used the rabbit infectivity test, identifying *T. pallidum* in the amniotic fluid of four of these eleven women. The study, however, failed to explain the mechanism by which *T. pallidum* entered the amniotic fluid and whether the fetus became infected by *T. pallidum* entering the placenta directly or by amniotic fluid intake or by an active mechanism of the fetus.

## Clinical Presentation of Congenital Syphilis

CS may cause fetal death, (presented as spontaneous abortion) generally after the first trimester of pregnancy,<sup>113</sup> stillborns; or may result in delivery of a premature newborn with evident signs of infection, or one who is completely asymptomatic.<sup>114</sup> Presentation of CS may be clinically similar to that observed after infection by cytomegalovirus, toxoplasma or rubella.<sup>115</sup> The clinical manifestations of CS can be classified into early and late stage manifestations. The early stage manifestations appear in the first 2 years of life.

### EARLY CONGENITAL SYPHILIS

When the fetus becomes infected, all the involved organs are affected due to dissemination of the treponemes. Hepatitis occurs as the earliest manifestation and may be diagnosed by finding increased transaminases in the fetal blood. Anemia and thrombocytopenia occur later and become evident through fetal hydrops or diffuse edema due to cardiac insufficiency, a negative Coombs result can help in the diagnosis.<sup>116</sup> Delay of intrauterine growth may also occur.

*Hepatomegaly* is the most frequent sign of early syphilis. Liver tests may be normal but jaundice caused by syphilitic hepatitis may develop with increased transaminases and alkaline phosphatase. Direct bilirubin may increase due to cholestasis. Prothrombin time could be increased.<sup>117</sup>

*Mucocutaneous manifestations* are observed in 70% of infected babies, at birth or develop during the first weeks of life. All mucocutaneous lesions have a large load of treponemes and are highly infectious.

Cutaneous manifestations include:

- Skin rash with bullae and desquamation in palms/soles (pemphigus syphiliticus): This is the most typical symptom. Tense



**Fig. 92.2:** Visceromegaly in a premature newborn with congenital syphilis. (Department of Neonatology, Instituto Materno Perinatal, Lima Perú. Courtesy of C. Velásquez).

vesicobullous lesions on palms and soles can be observed, with turbid and greenish content (Fig. 92.2). The vesicles break easily and leave the dermis unprotected. De-scaling occurs between the first and third week.

- Maculo-papular syphilides: occur on limbs and periorificial areas. The lesions are initially pink and evolve slowly and leave pigmentation (coffee and milk-colored spots). They resemble secondary syphilitic lesions in adults.
- Condylomata lata: may occur in mucous membranes or on the skin of areas affected by humidity or friction.
- Petechiae, in cases of severe thrombocytopenia.
- Anterior alopecia.
- Syphilitic paronychia (generally not involving the thumb).

The Syphilitic rhinitis or snuffles is a very common finding. A mucohemorrhagic secretion, as well as ulcerations on the upper lip and nasal vestibule are observed. It occurs in the first week of life. Even after treatment, these lesions may lead to permanent nasal deformities as sequelae.

Involvement of bones occurs in 60–80% cases of untreated CS, it is usually multiple and symmetrical, and resolves spontaneously within the first 6 months of life.

- Periostitis and cortical demineralization in the areas of long bone metaphysis and diaphysis (Fig. 92.3).
- Osteochondritis presenting in joints, mainly the knees, ankles, wrists, and elbows.
- Parrot pseudoparalysis: due to the pain by bone involvement the infected child will not move the affected limb.
- Wimberger sign caused by demineralization or destruction of the upper part of the metaphysis of the tibia which can be observed in x-rays.



\*c+



\*d+

**Fig. 92.3:** (a and b) Typical bullae and desquamation in palms and soles (pemphigus syphiliticus) of congenital syphilis. (Department of Neonatology, Instituto Materno Perinatal, Lima Perú. Courtesy of C. Velásquez)

Neurosyphilis can develop, frequently asymptomatic during the untreated neonatal period. The classical findings in the CSF in neurosyphilis are: a white blood count higher than  $25/\text{mm}^3$  (larger than  $200$  mononuclear cells/ $\text{mm}^3$ ), a protein count higher than  $150 \text{ mg/dl}$  ( $170 \text{ mg/dl}$  in premature babies), and a reactive VDRL.<sup>118</sup> Although sometimes, CSF results may be negative in spite of the neurological involvement, most of the CSF results are positive in symptomatic children and in 8% asymptomatic children. There are two forms of neurosyphilis:

- Acute syphilitic leptomeningitis is generally evident in the first months of life, with suggestive signs, such as those of acute bacterial meningitis (vomiting, enlarged fontanela, suture separation, increased cranial circumference). CSF results suggest an aseptic process. There is generally a good response to antibiotic treatment.<sup>119</sup>





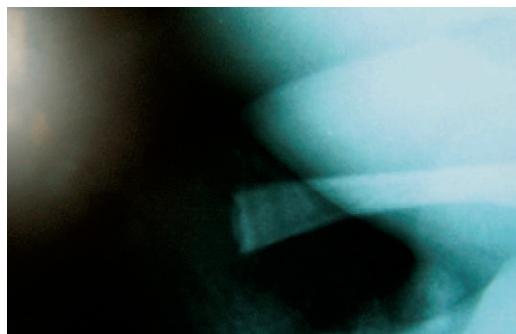
**Fig. 92.4:** Syphilitic pneumonia (pneumonia alba) and visceromegaly in a case of congenital syphilis. (Departament of Neonatology, Instituto Materno Perinatal. Lima Perú. Courtesy of C. Velásquez).

- Chronic meningovascular neurosyphilis generally occurs at the end of the first year of life, with signs of progressive hydrocephalus, paralysis of the cranial nerve, and regression of neuro-development. Seizures and cerebral infarction may occur in 2-year old children due to syphilitic endarteritis.

Other systemic abnormalities seen in CS include:

- Splenomegaly (Fig. 92.4) and periesplenitis.
- Corioretinitis with a tendency to congenital glaucoma and uveitis.
- Luetic glomerulopathy which is more likely of late occurrence since it is immunologically mediated (antigen–antibody deposit over the epithelial surface of the glomerulo basal membrane). Clinical manifestations are those of a nephritic syndrome or nephritis.
- Anemia, thrombocytopenia, leucopenia, and leucocytosis occur with relative frequency. Hemolytic anemia may persist after several weeks of effective treatment.
- Syphilitic aortitis (generally asymptomatic).
- Pneumonia alba (Fig. 92.5), named after the white color of the lungs due to fibrosing pneumonitis, which looks like a diffuse lung infiltrate in x-rays.
- Other findings include failure to thrive, pancreatitis, myocarditis, ileitis, gastrointestinal fibrosis, intestinal mass, and pituitary gumma.

The classic triad for early CS includes skin rash in palms/soles, snuffles, and hepatosplenomegaly.



**Fig. 92.5:** Femur with signs of epiphysitis and demineralization in a case of congenital syphilis. Departament of Neonatology, Instituto Materno Perinatal. Lima Perú. (Courtesy of C. Velásquez).

### LATE CONGENITAL SYPHILIS

The treatment for CS has contributed greatly to reducing the signs of late CS. When the infection is not diagnosed or treated during the neonatal period, 40% of the untreated children show manifestations of the destruction caused by the primary lesions and thus, these lesions will not be reversed by antibiotic treatment. The following are characteristic lesions associated to late CS:

- Saddle nose, due to the destruction of the bone cartilage.
- Olympic forehead, due to prolonged periostitis on the frontal bones.
- Higoumenakis signs due to thinning of the sterno-clavicular area of the sternum.
- Tibial thickening (sabre shin): hunching or bending the anterior curve of half of the tibia due to periostitis.
- Clutton joints, which are symmetrical, painless swelling of knees or elbows, usually after a trauma. Mobility is preserved and it is thought to be associated to perisynovitis which can resolve spontaneously.
- Perforation of the hard palate.
- Hutchinson teeth due to syphilitic vasculitis, occurring since birth, harming the adequate development of the teeth (clam-like, incisors with central excavation). Another sign is mulberry molars (first multicuspid molars).
- Deafness due to affection of the 8th nerve, occurs in approximately 3% of untreated cases, and often starts with the loss of high frequency hearing around 8–10 years of age
- Interstitial keratitis (normally between 5 and 20 years of age), secondary glaucoma or corneal scarring.
- Optic atrophy due to early retinal damage or hydrocephaly.
- Rhagades, cracks on the skin, which has lost elasticity. They are especially frequent around the mouth, anus or genitals, and derive from mucocutaneous damage at birth.

The Hutchinson teeth, interstitial keratitis, and deafness make up the classic Hutchinson triad which is typical of late CS.

### Laboratory Diagnosis

The diagnosis of CS is not an easy task. A combination of both clinical and laboratory approaches is frequently used. Overall,

all syphilis diagnostic laboratory tests fall into two categories: (i) indirect non-specific and specific serological tests and (ii) direct detection of whole organisms or their components. The currently available diagnostic procedures have limitations, and the sensitivity and specificity vary according to the specific method and the stage of the disease. Direct detection tests for whole organisms or their components include dark-field microscopy, rabbit infectivity test (RIT), direct fluorescent-antibody test and nucleic acid amplification. The diagnosis of CS is further complicated, especially in the asymptomatic newborn, by the fact that *T. pallidum* cannot be isolated in vitro and maternal antibodies cross the placenta. RIT is still considered the “gold standard” and is highly sensitive. However, it is most commonly used in research settings and is impractical and expensive as a routine diagnostic procedure.

Excellent guidelines and algorithms for the interpretation of syphilis serological testing of mother and infants, and treatment recommendation are widely available in the literature.<sup>120</sup> Here, we want to emphasize key issues rather than provide a lengthy description of diagnostic aspects that experts agree are relatively standard in the diagnosis of CS. Because clinical findings may not be characteristic of syphilis in the baby, confirmation of a case of CS requires demonstration of the syphilis spirochete in tissues or body fluids samples by microscopy, of anti-*T. pallidum* IgM antibodies, or by DNA or RNA amplification. The low sensitivity and the technical requirements of traditional methods explain the low percentage of confirmed cases of infected newborns. The addition of nucleic acid amplification promises, however, to increase the number of cases detected.

In settings with limited resources, a presumptive case of CS (lack of a definitive demonstration of the organism) is frequently the basis for treatment of newborns. Ideally, when diagnostic capabilities are available the “standard” diagnostic approach is: (i) to confirm infection of the mother with a specific test; (ii) to determine whether the mother was adequately treated; and (iii) to determine clinical or laboratory evidence infection in the fetus.<sup>121–125</sup> With limited resources, the presumption of transmission to the fetus is raised by a positive serology of the mother with no antenatal care or inadequately treated maternal syphilis. In this context, treatment of CS is recommended based upon a maternal positive non-specific treponemal test at pregnancy or delivery in combination or not with clinical symptoms of the newborn.<sup>126,127</sup> In health facilities with more technological resources, the presumptive diagnosis of CS is further supported by histopathological changes in placenta, umbilical cord, and fetus. Overall, in absence of direct demonstration of the syphilis spirochete in fluids or tissues, histopathological examination supports the diagnosis of transmission of *T. pallidum* from the mother to the fetus.

While serology is a cornerstone in the diagnosis of adult syphilis, standard serologic tests have low sensitivity in CS<sup>128–131</sup> and, when positive, they reflect the passive transfer of IgG antibodies to the fetus, which usually become undetectable in the infant after 12–18 months.<sup>132</sup> Because maternal IgM does not

cross the placenta, a positive specific anti-*T. pallidum* IgM test is diagnostic of CS. Measurement of total IgM in the newborn and FTA-ABS IgM test have proven to have low sensitivity and specificity.<sup>133–138</sup> An improved version of the FTA-ABS test (19S FTA-ABS IgM) was later developed in which IgM antibodies are purified over a HPLC column.<sup>139</sup> Both the 19S FTA-ABS IgM as well as a commercial capture-IgM versions show, however, poor sensitivity.<sup>140</sup> Other methods such as immunoblot analysis using either total *T. pallidum* lysates or recombinants have been developed,<sup>141–143</sup> but they are also technically demanding and are primarily used in research facilities.

The poor sensitivity of microscopy, serology or histopathology for the demonstration of *T. pallidum* has prompted the search for alternative more sensitive ways for identifying the syphilis spirochete in the newborn. End-point (conventional) nucleic acid amplification and real-time DNA and reverse transcriptase PCR (RT-PCR) have been developed over the years and are being applied for the diagnosis of syphilis including congenital infections. Such methods include single target and multiplex PCR. Several conventional DNA PCR techniques that target four single-copy genes have been described for the detection of *T. pallidum*.<sup>141–148</sup> The *T. pallidum*-specific PCR assays have been used with a wide range of samples, among others, intraocular specimens, testicular tissue, genital ulcers, blood, brain tissue, CSF, amniotic fluid, placenta, umbilical cord, fetal tissue, and serum samples.<sup>149–162</sup> Initial studies in CS showed good correlation of DNA PCR with RIT and IgM measurements.<sup>142,151</sup> In addition to end-point PCR assays, real-time PCR methods have been more recently developed<sup>163–167</sup> with very high reported sensitivities and specificities when compared to conventional serologic tests to diagnose early syphilis infection in adults. Although very promising, their usefulness, specificities, sensitivities, and positive predictive values in CS are yet to be determined.

Rapid, on-site diagnosis of maternal syphilis is an emerging field in the prevention and treatment of CS. Most pregnant women in countries with limited resources receive inadequate syphilis testing, mainly because of lack of on-site testing and the need to return to the health facility for follow up. The World Health Organization is actively promoting the use of rapid syphilis tests (RST) in resource-poor countries.<sup>168</sup> A rapid test is a simple point-of-care test that can be used in all health care settings to allow immediate treatment. Although RPR testing can be considered a rapid test, there are clear advantages of RST using *T. pallidum*-specific recombinant antigens. RSTs require minimal training, no refrigeration and no laboratory, are easy to administer, can be transported and stored below 30°C, and can be used with whole blood, serum or plasma with no prozone effect. In field settings, maternal syphilis can be diagnosed and treated at the point-of-care avoiding adverse outcomes due to delayed treatment.<sup>169–171</sup> Numerous studies show the usefulness of rapid tests<sup>172–183</sup> in the rapid identification and treatment of infected patients. Sabido et al.<sup>184</sup> demonstrated that the average total time spent by patients in a rural health facility for clinical interview, sample processing, RST results and treatment was 88.9 minutes.

Despite the concern of overtreatment, RST has the potential of diminishing adverse outcomes as well as improve cost-benefit issues in maternal and CS.

## Treatment

Benzathine penicillin G (BPG) remains the pharmacological treatment of choice for both acquired and CS, due to the relatively low serum concentration of drug (0.018 mcg/ml)<sup>185–187</sup> necessary to kill *T. pallidum*. Treatment with BPG has been shown to prevent both transplacental passage of *T. pallidum* and also to treat infection after it has occurred. In their study, Alexander et al.<sup>189</sup> followed a cohort of 340 woman treated for syphilis antepartum with a dose of 2.4 million units (MU) of BPG and reported that congenital transmission was prevented in 98% of patients, regardless the stage of syphilis, and in 95% and 98% of women with secondary and early latent infection, respectively. Treatment with BPG is also favored over erythromycin and azithromycin, in that penicillin resistance has never been reported in *T. pallidum*; on the contrary, infection with macrolide-resistant *T. pallidum* strains has been reported.<sup>190</sup> Although penicillin-binding proteins have been described and characterized in *T. pallidum*, these proteins are more likely involved in the synthesis and assembly of the bacterial cell wall rather for penicillin binding.<sup>191</sup>

## TREATMENT FOR MATERNAL SYPHILIS

Pregnant women with a reactive serologic test for syphilis should be treated with the BPG according to the stage of syphilis. (Table 92.5).<sup>188,189</sup> Since maternal syphilis is usually detected through a screening test during pregnancy, most of these women will be considered early latent or may be late latent syphilis. So national recommendations for their management suggest the use of BPG 2.4 MU IM as a single dose or three doses (one weekly) plus the treatment of the partner (US Preventive Services Task Force 2009). Since syphilis is a risk factor for both acquisition and transmission of HIV,<sup>192</sup> the patient should also be advised

**Table 92.5:** Treatment Guidelines for Acquired Syphilis during Pregnancy\*

Stage of infection	Regimen
Primary Secondary Early latent (≤1 yr)	Benzathine penicillin G, 2.4 million units (mU) total, administered intramuscularly (IM) in a single dose
Late latent (≥1 yr) Late syphilis of unknown duration	Benzathine penicillin G, 7.2 mU total, administered as three doses of 2.4 million units IM each at 1 week intervals
Neurosyphilis	Aqueous crystalline penicillin G, 18–24 mU/day, administered as 3–4 mU intravenously (IV) every 4 hours or continuous infusion, for 10–14 days. Alternatively, procaine penicillin G, 2.4 mU IM once daily and probenecid, 500 mg orally four times a day, both for 10–14 days can be used.

\*Source: CDC. Sexually Transmitted Diseases Treatment Guidelines, 2010

to undergo HIV antibody testing at the moment of diagnosis of syphilis infection. Although literature refers that approximately 10% of pregnant women with syphilis report a history of penicillin intolerance,<sup>193</sup> there is very little evidence of the harm of penicillin treatment, manifesting as severe allergic reactions.<sup>194</sup> Only one study<sup>195</sup> published recently provides information on serious adverse events of penicillin treatment, though this is based on a large US insurance claims database, and includes men (35%) and women (53%) and information specifically of pregnancy was not available. The incidence of anaphylaxis after penicillin was reported to be 0.1/10,000 doses; adverse effect of drug, 2.1/10,000 doses; allergy, 2.4/10,000 doses; and any allergic reaction, 4.7/10,000 doses. One limitation is that the penicillin was given orally, while the treatment for pregnant women is IM.

As shown by Wendel et al.,<sup>193</sup> skin testing, when possible, might be an effective way to assess penicillin allergy, and should be performed to prevent any risk of drug-induced anaphylaxis during treatment. In case of positive skin test, oral penicillin desensitization (procedure is described in Table 92.6) can temporarily induce tolerance to the drug in the patient before parenteral penicillin is administered. Desensitization to penicillin before treatment is currently preferred to alternative pharmacological treatments.

**Table 92.6:** Oral Desensitization Protocol for Patients with Skin Test-Assessed -Lactam Antibiotic Allergy\*

Step†	Amount of β-Lactam antibiotic (Units/mL) ‡	mL	Units	Cumulative dose (Units)
1	1000	0.1	100	100
2	1000	0.2	200	300
3	1000	0.4	400	700
4	1000	0.8	800	1500
5	1000	1.6	1600	3100
6	1000	3.2	3200	6300
7	1000	6.4	6400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700
15	After 30 minutes from the last dose, administer 800,000 U of the same agent IV.			

\*Source: Wendel GO Jr, Stark BJ, Jamison RB, Melina RD, Sullivan TJ. Penicillin allergy and desensitization in serious infections during pregnancy. *N Engl J Med* 1985;312:1229–32.

†Interval between doses: 15 minutes; elapsed time: 3 hours and 45 minutes; and cumulative dose: 1.3 million units.

‡The specific amount of drug was diluted in approximately 30 mL of water and then administered orally.



**Table 92.7:** Evaluation and Treatment of Infants for Congenital Syphilis\*

The following scenarios describe the evaluation and treatment of infants for congenital syphilis:

**SCENARIO 1.** Infants with proven or highly probable disease and an abnormal physical examination that is consistent with congenital syphilis, a serum quantitative non-treponemal serologic titer that is four-fold higher than the mother's titer<sup>†</sup>, or a positive darkfield or fluorescent antibody test of body fluid(s).

**Recommended Evaluation**

CSF analysis for VDRL, cell count, and protein.<sup>‡</sup>

Complete blood count (CBC) and differential and platelet count.

Other tests as clinically indicated (e.g., long-bone radiographs, chest radiograph, liver-function tests, cranial ultrasound, ophthalmologic examination, and auditory brainstem response).

**Recommended Regimens**

Aqueous crystalline penicillin G, 100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days. Alternatively, procaine penicillin G, 50,000 units/kg/dose IM in a single daily dose for 10 days.

If >1 day of therapy is missed, the entire course should be restarted. Data are insufficient regarding the use of other antimicrobial agents (e.g., ampicillin). When possible, a full 10-day course of penicillin is preferred, even if ampicillin was initially provided for possible sepsis. The use of agents other than penicillin requires close serologic follow-up to assess adequacy of therapy. In all other situations, the maternal history of infection with *T. pallidum* and treatment for syphilis must be considered when evaluating and treating the infant.

**SCENARIO 2.** Infants who have a normal physical examination and a serum quantitative non-treponemal serologic titer the same or less than four-fold the maternal titer and the mother was not treated, inadequately treated, or has no documentation of having received treatment; mother was treated with erythromycin or other non-penicillin regimen<sup>§</sup>; or mother received treatment <4 weeks before delivery.

**Recommended Evaluation**

CSF analysis for VDRL, cell count, and protein.<sup>‡</sup>

CBC and differential and platelet count.

Long-bone radiographs.

A complete evaluation is not necessary if 10 days of parenteral therapy is administered. However, such evaluations might be useful; a lumbar puncture might document CSF abnormalities that would prompt close follow-up. Other tests (e.g., CBC, platelet count, and bone radiographs) may be performed to further support a diagnosis of congenital syphilis. If a single dose of benzathine penicillin G is used, then the infant must be fully evaluated (i.e., through CSF examination, long-bone radiographs, and CBC with platelets), the full evaluation must be normal, and follow-up must be certain. If any part of the infant's evaluation is abnormal or not performed or if the CSF analysis is rendered uninterpretable because of contamination with blood, then a 10-day course of penicillin is required.

**Recommended Regimens**

Aqueous crystalline penicillin G, 100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days. Alternatively, procaine penicillin G, 50,000 units/kg/dose IM in a single daily dose for 10 days. Alternatively, benzathine penicillin G, 50,000 units/kg/dose IM in a single dose.

Some specialists prefer the 10 days of parenteral therapy if the mother has untreated early syphilis at delivery.

**SCENARIO 3.** Infants who have a normal physical examination and a serum quantitative non-treponemal serologic titer the same or less than four-fold the maternal titer and the mother was treated during pregnancy, treatment was appropriate for the stage of infection, and treatment was administered >4 weeks before delivery; and mother has no evidence of reinfection or relapse.

**Recommended Evaluation**

No evaluation is required.

**Recommended Regimen**

Benzathine penicillin G, 50,000 units/kg/dose IM in a single dose

**SCENARIO 4.** Infants who have a normal physical examination and a serum quantitative non-treponemal serologic titer the same or less than four-fold the maternal titer and the mother's treatment was adequate before pregnancy, and mother's nontreponemal serologic titer remained low and stable before and during pregnancy and at delivery (VDRL <1:2; RPR <1:4).

**Recommended Evaluation**

No evaluation is required.

**Recommended Regimen**

No treatment is required; however, some specialists would treat with benzathine penicillin G 50,000 units/kg as a single IM injection, particularly if follow-up is uncertain.

\*Source: CDC. *Sexually Transmitted Diseases Treatment Guidelines*, 2010

<sup>†</sup>The absence of a four-fold or greater titer for an infant does not exclude congenital syphilis.

<sup>‡</sup>CSF test results obtained during the neonatal period can be difficult to interpret; normal values differ by gestational age and are higher in preterm infants. Values as high as 25 white blood cells (WBCs)/mm<sup>3</sup> and/or protein of 150 mg/dL might occur among normal neonates; some specialists, however, recommend that lower values (i.e., 5 WBCs/mm<sup>3</sup> and protein of 40 mg/dL) be considered the upper limits of normal. Other causes of elevated values should be considered when an infant is being evaluated for CS.

<sup>§</sup>A woman treated with a regimen other than those recommended in these guidelines for treatment should be considered untreated.

<sup>¶</sup>If the infant's nontreponemal test is nonreactive and the likelihood of the infant being infected is low, certain specialists recommend no evaluation but treatment of the infant with a single IM dose of benzathine penicillin G 50,000 units/kg for possible incubating syphilis, after which the infant should receive close serologic follow-up.

<sup>†</sup>Some specialists would not treat the infant but would provide close serologic follow-up in those whose mother's nontreponemal titers decreased four-fold after appropriate therapy for early syphilis or remained stable or low for late syphilis.

Tetracycline and doxycycline are generally contraindicated during pregnancy in that they impair long-bone development and stain decidual teeth in the newborn.<sup>196</sup> Furthermore, tetracycline can cause hepatic toxicity when renal dysfunction is already present. The use of erythromycin instead of BPG is currently not advised due to the increasing reports on macrolide resistance exhibited by *T. pallidum* strains.<sup>190</sup> Concern for use of erythromycin is also associated with the possible erratic transplacental transfer of the drug to the fetus.<sup>197–199</sup> Currently, no data are available to support the use of azithromycin or ceftriaxone to treat CS.

Several hours after treatment with BPG has begun, adult patients might manifest the symptoms of the Jarisch–Herxheimer reaction, which consist of fever, myalgia, headache, hypotension, tachycardia, and transient exacerbation of cutaneous lesions.<sup>186</sup> Such manifestations normally last for 24–36 hours and are currently hypothesized to be caused by the release of proinflammatory components (i.e., lipoproteins, since *T. pallidum* does not synthesize lipopolysaccharide)<sup>200–203</sup> by dying and/or killed treponemes. In pregnant women, the Jarisch–Herxheimer reaction has also been associated<sup>1204</sup> with intrauterine contraction; episodes of tachycardia and deceleration in the fetus heartbeat and overall decrease of fetal movement. Wendel<sup>196</sup> suggested that women diagnosed with syphilis that have already entered their third-trimester pregnancy should undergo sonographic evaluation of the fetus condition and, if hepatomegaly or signs of hydrops are detected, they should be hospitalized for fetal monitoring during the first 24 hours following penicillin administration. If evidence of fetal compromise is detected before penicillin administration, physicians should consider delivering the infant by caesarian section and then treating both mother and newborn separately.<sup>196</sup>

Prolonged treatment of the infant after childbirth could be necessary if treatment of the mother was started within the last 4 weeks of pregnancy. It is possible, in fact, that if penicillin administration is started during the last weeks of pregnancy, the physiological phenomena that accompany pregnancy progression (i.e., increased renal clearance and plasma volume) might alter penicillin pharmacokinetics and result in lower serum and CSF concentration of BPG in both mother and fetus and diminish the effectiveness of the treatment during the final stage of pregnancy.<sup>205</sup>

## TREATMENT OF THE NEWBORN

The diagnosis of CS is complicated by the transplacental transfer of maternal non-treponemal and treponemal antibodies to the fetus. Treatment decisions must be made on the basis of several criteria, which include identification of syphilis in the mother, adequacy of maternal treatment, presence of clinical, laboratory, or radiographic evidence of syphilis in the infant; and comparison of maternal (at delivery) and infant non-treponemal serologic titers.<sup>187</sup> All infants born to mothers who have reactive non-treponemal and treponemal test results should be evaluated with

a quantitative non-treponemal serologic test performed on infant serum because umbilical cord blood can become contaminated with maternal blood and could yield a false-positive result. Conducting a treponemal test on a newborn's serum is not necessary. All infants born to women who have reactive serologic tests for syphilis should be examined thoroughly for evidence of CS.<sup>187</sup> Pathologic examination of the placenta or umbilical cord by using specific fluorescent anti-treponemal antibody staining is suggested. Dark field microscopic examination or DFA staining of suspicious lesions or body fluids (e.g., nasal discharge) also should be performed.<sup>187</sup> Each of the scenarios described in Table 92.7 leads to a recommended evaluation and treatment of the newborn. In limited resource settings, if there is evidence of untreated maternal syphilis, the newborn should be treated.<sup>78</sup>

## FOLLOW-UP MANAGEMENT

Seroreactive infants should receive a non-treponemal test every 2–3 months until the test becomes non-reactive or the titer has decreased four-fold.<sup>187,206,207</sup> If the infant was not infected, and the reactive test result was caused by passive transfer of maternal IgG antibody, non-treponemal antibody titers should decline 3 months after birth and should be non-reactive after 6 months.<sup>187</sup> The same trend should be expected if the infant was infected but adequately treated. The serologic response after therapy might be slower for infants treated after birth. If these titers are stable or increase after age 6–12 months, the child should be evaluated again for syphilis, given a CSF examination, and treated with a 10-day course of parenteral penicillin G.<sup>187</sup> The use of treponemal tests to evaluate treatment response is not recommended, because an infected child can remain positive despite effective therapy in that passively transferred maternal treponemal antibodies can be present in an infant until 15 months of age. A reactive treponemal test after 18 months of age is diagnostic of CS. If the non-treponemal test is non-reactive at this time, no further evaluation or treatment is necessary. If the non-treponemal test is reactive at age 18 months, the infant should undergo reevaluation and treatment for CS.<sup>208</sup> Infants whose initial CSF evaluations are abnormal should undergo a repeat CSF evaluation approximately every 6 months until the results are normal. A reactive CSF VDRL test or abnormal CSF indices that cannot be attributed to other ongoing illness requires retreatment for possible neurosyphilis.<sup>187</sup>

### Summary

Congenital syphilis (CS) is still a public health problem. According to WHO more than two million pregnant women are infected with syphilis and up to 69% of those not treated will result in adverse pregnancy events, and CS. Screening of pregnant women for syphilis and treatment with penicillin is an effective measure to prevent CS. Rapid, on-site diagnosis with rapid syphilis tests is a cost-effective tool for screening.

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## Introduction

About 80–90% of fertile couples achieve pregnancy within 1 year and 95% within 2 years of regular, unprotected intercourse. Approximately, one in six couples (15%) face the problem of infertility at sometime in their reproductive lives and seek advice of a gynecologist,<sup>1</sup> attend a family planning or infertility clinic.

Infertility is defined as the inability to conceive in 1 year of regular co-habitation without using any contraceptive. Infertility is primary when the woman has never been pregnant and secondary when the woman fails to conceive following one or more pregnancies or abortion/miscarriage. The problem of infertility involves one or both the partners who need to be investigated simultaneously, counselled, and treated appropriately. This saves time and is cost effective.

Main causes of infertility in women include decreased ovarian reserve, ovulatory disorders, tubal injury (blockage or paratubal adhesions), uterine factors, immunological aberration, or a systemic illness. Important causes of infertility in males include genital injury, infections of semen, testes and accessory glands, genital tract obstructions, varicocele, genital malformations, endocrine and metabolic diseases, drug use and abuse, and psychiatric conditions. Primary infertility mostly can be due to chromosomal abnormality, congenital malformation and or endocrinopathies or can be idiopathic. STI pathogens cause pelvic inflammatory disease (PID) leading to tubal blockage, which is mostly responsible for secondary infertility in female. Tubal factor in infertile women accounts for 30% of the cases. There is a suggestion in the literature that genital tract infection or STI could damage hemato-testicular barrier and elicit formation of antisperm antibodies. Secondary infertility due to STIs is more common and is primarily due to chlamydial or gonococcal causes leading to PID–tubal factors.

Several data-based evidences indicate that sexually transmitted infections reduce fertility both in males and females. STD-related infertility occurs three times more often in Africa than in other parts of the world. STIs affect human fertility primarily through infections of the female upper genital tract and less frequently, through obstructions of vas deferens in the male.

It is important to know that in most of the developing countries normal gynecological check up does not include routine testing for important STIs like *Chlamydia trachomatis* or gonorrhea that are most likely to affect fertility.

Many young people do not seek treatment because of fear of public disclosure, associated shame and guilt and repercussions from angry parents and community elders. Asymptomatic nature of the disease does not allow early detection and treatment of these infections, thus leading to their sequelae like PID and infertility as a result.

## Epidemiology

Though a link between STIs and infertility has been known far more than a century, the high magnitude of STI-related infertility has only been appreciated lately throughout the world. Sub-Saharan Africa has the highest prevalence of STI-related infertility. A study between 1979 and 1984 in 25 countries revealed that as many as 64% infertile couples were afflicted with a STI in Africa and up to 38% in other parts of the world.<sup>1</sup> In USA, over 100,000 women become infertile each year because of PID.<sup>2</sup> The risk factors for acquiring these infections are young age at the commencement of sexual activity, multiple sex partners, non use of barrier contraceptives, and low socio-economic status. Sex workers and those infected with HIV are at the highest risk.<sup>3,4</sup> Sexually transmitted infections may cause infertility by several mechanisms in both males and females, and different organisms influence fertility in different ways. (Table 93.1, 93.2 and 93.3)

**Table 93.1:** Organisms Affecting Fertility

- *Chlamydia trachomatis*
- *N. gonorrhoea*
- *Trichomonas vaginalis*
- Bacterial vaginosis
- HIV infection
- HPV
- HSV
- *M. hominis*, *U. urealyticum*, *M. genitalium*

**Table 93.2:** The Organs Involved and Clinical Features

Men
Primary site: urethra
Secondary site: upper genital tract, testes
Clinical feature: infertility due to blockage of the passage and sperm dysfunction
Females
Primary site: cervix
Secondary site: upper genital tract
Clinical: infertility, ectopic pregnancy, chronic pelvic pain and PID

### Etiological Organisms/Sexually Transmitted Agents that may Cause Infertility

The main sexually transmitted organisms responsible for infertility are *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (CT). Syphilis may cause infertility, but normally this disease is associated with bad obstetric history in the form of late abortions, stillbirth, and neonatal syphilis.

*Trichomonas vaginalis* although is a sexually transmitted pathogen but its impact on fertility is minimal. *Mycoplasma hominis*, *Ureaplasma urealyticum*, aerobes, and anaerobes are present in the genital tract, but are not usually transmitted sexually. They may act as co-factors in those who have acquired a STI and indirectly contribute to infertility by further damaging the structures in the genital tract.<sup>3,4</sup> Less frequently male infertility is due to epididymo-orchitis, mostly caused by *Escherichia coli*. Uropathogenic *E. coli* are more likely than commensal *E. coli*

to be shared with a current heterosexual sex partner. Both sexual behaviors and a bacterial virulence factor can cause the disease.<sup>5,6</sup>

Viruses like HIV, HSV, and HPV though have no direct effect on genital tract, may not cause inflammation but may contribute to infertility by affecting the sperm count and motility and worsening the course of other co-existing STIs.

### Pathogenesis of Infertility

#### IN MALES

Infections of male genito-urinary tract account for about 15% of the case of male infertility.<sup>1</sup> Infections can affect different sites of the male reproductive tract, such as the testis, epididymis and male accessory sex glands. Spermatozoa themselves subsequently can be affected by urogenital infections at different levels of their development, maturation, and transport by several mechanisms, such as sperm nuclear condensation, nuclear fragmentation, decreased sperm motility, and apoptosis.<sup>7</sup>

#### IN FEMALES

Acute cervicitis caused by *N. gonorrhoeae* and/or chlamydia if it causes symptoms is treated promptly. Asymptomatic and chronic cervicitis form a reservoir for bacteria and can impair sperm functions as the sperms move up to the fallopian tubes. Aerobic and anaerobic organisms normally present in the vagina also ascend in a piggy-back fashion with these organisms setting up

**Table 93.3:** Summary of the Possible Associations Between Some Microbiological Agents and Infertility

Microorganism	Female infertility			Male infertility		
	Cervical/vaginal	Uterine	Tubal/pelvic	Testes/epididymis <sup>a</sup>	Prostate/accessory glands	Semen alterations/sperm damage
<i>C. trachomatis</i>	Definite	Definite	Definite and very common	Definite	Doubtful	Possible
<i>N. gonorrhoeae</i>	Definite, but less studied	Definite	Definite	Definite	Probable	Probable
<i>M. hominis</i>	Probable	Possible	Still to be defined	Doubtful	Doubtful	Doubtful
<i>U. urealyticum</i>	Probable	Possible	Still to be defined	Doubtful	Doubtful	Doubtful
<i>M. genitalium</i>	Probable	Possible	Most probable	Doubtful	Doubtful	Attaches to human sperm
Bacteria associated with vaginosis	Possible	Possible	Probable; no associations with specific organisms	Doubtful	Doubtful	Doubtful
<i>T. vaginalis</i>	Possible cofactor	Doubtful	Possible cofactor	Doubtful	Doubtful	Probable under specific conditions
Human papilloma virus	Defined through CIN	Defined through CIN	Improbable	Doubtful	Doubtful	Association needing further investigation
Herpes simplex virus	Doubtful	Doubtful	Association needs further investigations	Doubtful	Doubtful	Probable

Modified from Pellati et al. 2008.<sup>49</sup>



secondary infections in the fallopian tubes. Chlamydial infection is asymptomatic in female in 75% cases, but it causes devastating damage to the fallopian tubes much more than that caused by gonorrhea.

Initially, these bacteria cause endosalpingitis. During the healing process, adhesions form in the lumen. Extensive damage causes fibrosis and peritoneal adhesions leading to tubal blockage or narrowing and stricture formation. All these result in tubal infertility, ectopic pregnancy, and chronic pelvic pain. The external adhesions are seen in the form of fibrous band extending from the right fallopian tube to the undersurface of the liver known as Fitz–Hugh–Curtis syndrome, or perihepatitis.

PID is a clinical syndrome of polymicrobial etiology responsible for tubal damage in 30–40% of infertile women. The rising incidence of PID in recent years strongly correlates with increasing prevalence of STIs and tubal-related infertility.<sup>1</sup> It was observed that 17% women with clinical evidence of PID diagnosed laparoscopically were infertile as compared to none who did not suffer from PID. The proportion of women with infertility was dependent on the number of episodes of PID, its severity and type of organisms involved.<sup>8</sup> In the developed countries, 75% women below 25 years who developed PID were found to have suffered from STIs. The tubal block occurred in 12.8% of patients following one attack of PID, 40% with two attacks and as many as 75% following three or more episodes.<sup>4,8,10</sup> On investigating the association between the lower genital tract infection and infertility, it was observed that most women with tubal infertility did not reveal a history of acute pelvic infection, but sub-clinical PID with mild abdominal pain was observed in 27%.<sup>10,11</sup>

In developing countries, genital tuberculosis in females adds to tubal infertility but this is not supposed to be sexually transmitted.

## N. GONORRHOAE

### In Males

Until recently, *N. gonorrhoeae* was the commonest genital infection. Initially, this infection is limited to the lower genital tract causing urethritis and epididymitis. The diagnosis is easy by studying urethral swab, using Gram-stain, culture, and a NAAT. In a smear, gram-negative intracellular kidney-shaped diplococci are recognized. Prompt treatment cures acute infection. If untreated, the infection spreads to the upper genital tract and causes orchitis and testicular dysfunction. The blocking of the vas leads to oligo- or azoospermia. Unilateral epididymo-orchitis is associated with 23% infertility, whereas bilateral infection causes infertility in 40% cases.<sup>12</sup>

### In Females

In females, *N. gonorrhoeae* was the most common STI accounting for up to 50% tubal infertility in the preantibiotic era. The incidence now has dropped to 10–15%. In UK, its incidence is as low as 10/1000 in women between 15 and 29 years of age.

Recently, penicillinase-producing *N. gonorrhoeae* (PPNG) that causes management problem is becoming more prevalent in south and South-East Asia and Africa. These organisms are transported to other countries through travelers.<sup>9,11</sup> Various studies reveal that 27–39% cases of PID are now caused by chlamydia and 19–26% by *N. gonorrhoeae*.<sup>3,10</sup>

*N. gonorrhoeae* initially causes urethritis, cervicitis and salpingitis. During the healing process, the mucosal adhesions narrow the tubal lumen or cause blockage and peritoneal adhesions. The reduced frequency of coitus due to dyspareunia produced by pelvic inflammatory mass contributes to infertility. Cytokines IL-1a, IL-1b, and TNF- $\alpha$ , produced by tubal epithelial cells after challenge with *N. gonorrhoeae*, may contribute to the genesis of gonococcus-induced infertility.

*N. gonorrhoeae* also helps other organisms present in the vagina to ascend to the fallopian tubes and set up secondary infection. Once this happens, it is difficult to detect and culture *N. gonorrhoeae* from the tubal secretions. Early treatment can prevent tubal damage. In developed countries, PID due to gonococcal infection has declined considerably due to early treatment as well as preventive measures like barrier contraceptives.

## CHLAMYDIA TRACHOMATIS (CT)

*C. trachomatis* is an obligate intracellular bacterium and has a biphasic life cycle characterized by an elementary body (EB) with infective capacity and reticular body (RB) that replicates in eukaryotic cells. *C. trachomatis* has a worldwide distribution, affecting both sexes but has a much greater impact on females than on males. Chlamydial infections may, in many cases, remain silent. This pathogen particularly affects young women and sexually active adolescents. Serovars A, B, Ba, and C are associated with endemic trachoma, while serovars L1, L2, and L3 are associated with lymphogranuloma venereum (LGV). Serovars D through K are the major causes of non-gonococcal urethritis and epididymitis in men and may induce Reiter syndrome, proctitis, and conjunctivitis in both men and women, and cervicitis, urethritis, endometritis, salpingitis, and perihepatitis in women.

### In Females

*C. trachomatis* is believed to be one of the major causes of cervical factor infertility, as a result of the alterations of the epithelium and mucus composition, and by the presence of inflammatory cells; although, the overall impact of cervical disorders on fertility still needs to be assessed. Keltz et al.<sup>11</sup> reported chlamydia to be the most common cause of tubal infertility with 296.5 cases per 10,000 population in United States. Amongst PID cases, 30% of the hospitalized cases and 50% of OPD cases had chlamydial etiology.<sup>14</sup> Another study observed this organism in 53% of women with PID.<sup>15</sup> Most women with chlamydial infection are young and sexually active. Up to 70–75% of them are asymptomatic.<sup>16</sup>

Acute cervicitis is frequently a self-limiting condition, remains asymptomatic, unnoticed and therefore untreated.<sup>17,18</sup> In 20%, the

infection ascends to the upper genital tract and sets up chronic PID. It then causes more extensive damage to the fallopian tubes as compared to that caused by gonorrhea.<sup>8</sup>

Chlamydiosis is a major cause of tubal obstruction and ectopic pregnancy, and can result in PID, adnexitis, local or diffuse peritonitis, and formation of adhesions which may disrupt the passing of oocytes through the tubes; so this infection in women interferes seriously with human reproduction. The fact that such conditions often occur in adolescents and may preclude them from having a reproductive future, has put this infection under the spotlight.<sup>19</sup> The chlamydial 10 and 57 kDa HSP (cHSP10 and cHSP57/60, respectively) show remarkable homology to human proteins. Thus, this expected cross-reactivity between the human HSP60 and the bacterial cHSP60 leads to the formation of antibodies against the HSP60 in the serum and follicular fluid of women exposed to *C. trachomatis*. High homology to a human protein may cause autoimmune infertility that can make even IVF ineffective.

These antibodies also have a negative impact on embryonal growth, and increase the probability of adverse pregnancy outcomes. HSP57/60 also has been found to induce trophoblast apoptosis by stimulating the toll-like receptor 4 (TLR4), which naturally mediates immune responses in placenta.<sup>18</sup> Women with serum antibodies against HSP60 and positive for *C. trachomatis* seem to have a greater probability of tubal scarring and ectopic pregnancy, compared to women who are only seropositive for anti-chlamydial antibodies. There also seems to be a cross-reactivity between HSP10 and an embryonic protein, the early pregnancy factor (EPF), and this may cause abortions. cHSP10 too, probably correlates with the severity of the disease in women and so with the presence of tubal factor infertility.<sup>20</sup> HSP60 has consequently been proposed as a prognostic criterion for the assessment of chlamydial infections in women and, together with other humoral parameters, as a means for a prior diagnosis of tubal factor infertility.<sup>21</sup> Genetic conditions involving immune regulation pathways may have an important role in the whole process of *C. trachomatis*-induced damage. Some variants of the gene that controls IL-10 production may be involved in the impairment of the immune response against the bacterium.<sup>22</sup> Finally, a strong antibody response against *C. trachomatis*, but no sign of current or chronic infection was found in women with tubal factor infertility (TFI), indicating that previous infections may have resulted in permanent damage and occlusion of the fallopian tubes. Antibodies to *C. trachomatis* were present in 23% of women with tubal factor infertility as compared to the figure of 15% in women with normal tubes. None of the infertile women had evidence of infection in the past.<sup>16</sup> While these small studies fairly suggest an association, there have not been the detailed longitudinal studies that would allow accurate estimates of the actual risk of infertility after *C. trachomatis* infection.

Given the potential for morbidity from ectopic pregnancy and tubal infertility the case for screening for chlamydia among those most at risk is strong.<sup>23</sup> Enzyme immunoassays for detecting chlamydial antigen and direct nucleic acid probe assays are the most

widely used and can evaluate large number of samples. Nucleic acid amplification tests for chlamydia, including polymerase chain reaction and transcription-mediated amplification assays, are more sensitive and highly specific. Although there is no absolute “gold standard” for chlamydia tests, amplification assays have a sensitivity of at least 90% compared with 60–70% for culture and 60% for antigen assays.<sup>23</sup>

Treatment with a single oral dose of azithromycin 1g or doxycycline 100 mg twice daily for 7 days eradicates acute infection. However, recurrences do occur. Therefore, vaccine against this infection is suggested as the only option. More research and development of vaccine may be the answer if tubal infertility due to *C. trachomatis* is to be prevented before infection is acquired.<sup>17</sup>

## In Males

In males, with decreased prevalence of gonococcal infections, *C. trachomatis* is now the commonest bacterial infection causing infertility. Epidemiology of CT infection in a male is difficult to evaluate because 50% men remain asymptomatic and organisms grow only in tissue culture.<sup>24</sup> With the availability of sensitive NAATs and serum and semen antibody estimation, the importance of this organism is being increasingly recognized.

*C. trachomatis* can be detected in the urethral swab and urine, when urethritis occurs. It is however difficult to detect chlamydial DNA in the secretions of the male accessory glands. IgG and IgA antibodies in the serum and semen are then the only evidence of infection in the upper genital tract.<sup>25,26</sup> By routine testing for chlamydia in infertile couples, Bennett et al.<sup>27</sup> revealed evidence of infection in 39% males. A study of 40,094 men from a STD clinic revealed prevalence of CT in 10.3% men below 29 years of age.<sup>27</sup> In another study, CT infection was seen in as much as 8.3% of male partners of infected couples as compared to only 2.5% in the control group.<sup>28</sup> More than 101 million new cases of chlamydia occur each year world wide (WHO 2005), but as mentioned earlier, 75% infected women and 50–70% men remain symptom less and are not recognized. In one study, infection accounted for 15% cases of male infertility.<sup>7</sup>

Acute infection causes urethritis, but this does not interfere with fertility of those fully treated. Chronic infection can cause damage at various sites in the genital tract and by different mechanisms. The evidences suggest that in the humans *C. trachomatis*, causes infertility by a route independent of structural damage to the genital tract. This is shown by *in vitro* studies.<sup>29</sup> The primary site of infection is the urethra, causing urethritis in 30–40% in men. The urethral swab and urine culture can detect its presence. Epididymitis follows in 40–50%, but uncontaminated specimen is difficult to obtain for its detection.<sup>25</sup> A causative link between chlamydia and epididymo-orchitis has been reported in 11–35% of men. The presence of antibodies in the semen and serum indicate past infection. The chlamydia attaches to the leukocytes and sperms as shown by electron microscopy and this is responsible for transmission of infection to the female partner.

Evidences based till date have shown that chlamydia causes increased semen volume and pus cells thereby indicating

inflammation and release of cytokines. It decreases the sperm motility and causes apoptosis (death) by its lipopolysaccharide component which has spermicidal effect. The measurable intracellular changes in the tyrosine phosphorylation of sperm protein in response to the bacteria are also detrimental to the sperm functions.<sup>30,31</sup> Fragmentation and sperm nuclear condensation interfere with fertilization process. Dimitrova et al.<sup>26</sup> proved that CT can provoke formation of anti-sperm antibodies that impair fertility. A few studies<sup>7,29</sup> however have denied any detrimental influence of chlamydial infection on fertility, but this can be explained on account of different methods used to obtain specimens and tissues for its detection. Most studies conclude chlamydial infection as one of the important additional causes of infertility both in men and women.

### TRICHOMONAS VAGINALIS

*T. vaginalis* has a worldwide distribution and is a common infection of the male genital tract. It can rarely cause urethritis and perhaps prostatitis and other genital tract disorders. Evidence suggests that men with trichomoniasis have decreased sperm motility, more abnormal sperms, higher semen viscosity and particulate debris, and diminished integrity of the spermatozoan membrane.<sup>32</sup> However, long-term consequences of trichomoniasis are unknown, and overall evidence suggests that its impact on male fertility may be minimal.<sup>33</sup> The clear association between the presence of *T. vaginalis* and leukorrhea, and the significant association with bacterial vaginosis, have suggested that the presence of trichomonads might have a favorable effect on bacterial growth. Trichomoniasis is associated with mild vaginal and cervical damage, and does not seem capable of producing cervical factor infertility. It has also been associated with adverse pregnancy outcomes.<sup>34</sup> Other than bacterial vaginosis, *T. vaginalis* promotes the action of *M. hominis* by transporting the bacterium inside the protozoa cell and by permitting its active replication. This offers protection to the bacterium from the action of the immune system and the effects of therapies, and favors its spread by transporting it through the genital tract, as a clear and important example of a symbiotic relationship between human pathogens.<sup>35,36</sup>

### MYCOPLASMAS

The role of *M. hominis* and *U. urealyticum* is less clear. These are residents of the lower genital tract in 50% of sexually active females. However, only 7% are involved in PID. They may act as co-factors associated with other infections.<sup>10,16</sup>

*Mycoplasma genitalium* is another organism that has recently been found to be sexually transmitted and is harmful to both the sexes. It is isolated from urine in the male and is known to cause non-gonococcal urethritis. It is present in 56% of male partners with infected women and 32% among female partners of infected males. In a study from Denmark, antibodies to *M. genitalium* were present in 17% of the women with tubal factors infertility as compared

to the figure of 4% for women with normal tubes.<sup>16</sup> The difficulty in detecting its presence lies in the limitations of cultivating the organism and non-availability of commercial serological kits. The slow growing nature of *M. genitalium* allows overgrowth of other organisms. PCR is now employed to detect this mycoplasma. A British study showed 13% women with PID were PCR positive for this organism, compared to the control group.<sup>37</sup> In Kenya, 7% with laparoscopically proved PID were PCR positive. *M. genitalium* can grow independent of *N. gonorrhoeae* and chlamydia. *M. genitalium* is strongly associated with cervicitis, endometritis, and serologically with salpingitis-pelvic inflammatory disease (PID), and may account for a number of cases of infertility.<sup>16,37</sup>

*U. urealyticum* is associated with the production of reactive oxygen species, even in absence of leukocytospermia, and *M. genitalium* can attach to human spermatozoa and thus could be carried out by motile sperm. This ability may be important in the process of causing female genital diseases and infertility.<sup>38</sup>

### GARDNERELLA VAGINALIS

*G. vaginalis* seems to be very common in the genital tract of men with suspected infertility, and is also frequent among infertile men and even more among their wives; the significance of this data, however, remains unclear since the bacterium is also common amongst normofertile individuals.

Bacterial vaginosis (BV) in a woman is not uncommon, but the role of the organisms responsible for BV in infertility is not clear. Microorganisms associated with bacterial vaginosis, apart from *M. hominis* and *U. urealyticum*, include *G. vaginalis*, *Mobiluncus* spp., *Bacteroides* spp. (excluding *Bacteroides fragilis*), *A. vaginae*, and *Peptostreptococcus* spp. and may reach the genital tract in several manners. There is the speculation that these organisms adversely affect the quality of sperms deposited in the vagina and their fertility potential.<sup>39</sup> Wiesenfel et al.<sup>10</sup> reported that 15% women with BV developed endometritis and PID. These organisms not only cause tubal damage, but also interfere with implantation of the fertilized egg.

### VIRUSES

#### Human Immunodeficiency Virus

HIV may impair semen parameters by itself and certainly deteriorates the outcome of concomitant genital infections; in addition, the specific anti-HIV therapies can damage the male reproductive system. In a study of 24 HIV-positive and 60 HIV-negative men, HIV-infected men had substantially reduced sperm counts and increased number of abnormal sperms.<sup>40</sup> Furthermore, semen parameters of HIV-infected men are inversely correlated with the extent of disease progression.<sup>41,42</sup>

HIV has a negative impact also on female fertility, but it is not clear to what extent this is due to the activity of the virus itself, or to other genital infections, whose course is adversely affected in the presence of HIV infection, or even to the side effects of therapies. In endemic regions of Africa, HIV infection appears to reduce



female fertility by 16–26%, producing higher rates of involuntary childlessness and longer intervals between births.<sup>43</sup> Tubal disease among HIV-infected women appears to be secondary to infection with other STIs, such as chlamydial infection or gonorrhea. HIV infection may affect the hypothalamic-pituitary-ovarian axis, causing sub-fertility secondary to hormonal dysfunction. However, these changes have not been observed consistently.<sup>44</sup> If HIV infection produces hormonal dysfunction, it may occur only as the disease progresses to more advanced stages. Recent progress on antiretroviral therapies and on assisted reproduction techniques has made the birth of healthy children from seropositive parents possible.<sup>45</sup>

## Herpes Simplex Virus

The presence of HSV DNA in human spermatozoa, even if in low percentage, was significantly related to poor sperm count and reduced motility.<sup>46</sup> Antiviral treatment of male infertility patients positive for HSV in semen resulted in successful pregnancies. Thus, HSV infection of the male genital tract could explain some cases of male infertility, as a consequence of its association with decreased semen quality.<sup>47</sup>

A significant association seems to exist between serum IgM antibodies against HSV, and the presence of leukocytospermia, although the clinical significance of the later condition still remains unclear. HSV infections, on the other hand, seem to have no significant association with cervical factor infertility.<sup>47</sup> Cherpès et al. indicate a possible association with PID, without specifying the way in which the virus may be involved in the pathogenesis of the disease.<sup>48</sup>

## Human Papilloma Viruses (HPV)

HPVs were found in testicular biopsies of azoospermic men and when present inside sperm cells, they may be related to impaired sperm motility and asthenozoospermia.<sup>49</sup> Alvarez Fernandez et al. found, in 1998, an association between HPV and infertility, particularly between the presence of these agents and tubal factor infertility, and such association, according to the researchers, necessitates further investigations.<sup>50</sup> Obviously these viruses are much more harmful in the cervical region. Surgical procedures for cervical intraepithelial neoplasia (CIN), though less invasive nowadays, still cause cervical mutilations that compromise fertility.

## Prevention

With the above observations, it is clear that most sexually transmitted infections do contribute to infertility to a variable extent by several mechanisms both in the male and female. In New Zealand, the screening program for chlamydia has reduced the incidence of infection by 50%.<sup>27</sup> Therefore some have suggested screening should also be extended to infertile couples.

Early detection and treatment of asymptomatic cases will prevent ascending infection which really impairs fertility. Sex education to young couples and adolescents indulging in sexual activity and motivating them to use barrier contraceptives will

be a step forward in reducing sexually transmitted infections.<sup>51</sup> In IVF program checking for chlamydia would improve the success rate.

## Conclusion

Infections can damage reproduction in diverse ways. The complexity of these mechanisms can create confusion for epidemiologists interested in the causation of reproductive impairments. For example, chlamydial infection causes infertility through tubal scarring. By the time the infertility is manifest (often years later), the infection has usually been cleared. Meanwhile, other factors associated with chlamydial infection, such as other STIs, social habits of affected women, or environmental conditions, may mistakenly be blamed for the women's decreased fertility.

These complexities raise interesting questions for epidemiologists who study reproduction. For a given infectious agent and outcome: is it prior infection, latent infection, or active infection that is most important? Is it the severity of the infection or the strength of the immune response that damages reproduction? Might non-infectious factors of interest increase the risk of reactivation of a latent infection, or increase the risk of a new infection? Are there risk factors that confound the relation of an infection with the outcome? Are there infections that confound the study of non-infectious exposures and their relationship to fertility or pregnancy?

Although both men and women risk serious consequences, the female reproductive potential seems to be much more at stake. Tubal-pelvic factor infertility has rightfully gained attention as the greatest hazard deriving from infectious diseases.

*N. gonorrhoeae* and chlamydia are mostly responsible for genital tract infections and STI-related infertility. With the incidence of gonorrhoea declining, *C. trachomatis* is the pathogen that has been most intensely related to these particular fertility disorders, and is still considered to be a major social hazard. Acute infections usually do not impair fertility, but a chronic infection, by virtue of damage to the genital tract and impairing sperm morphology and functions can lead to infertility. Unfortunately, 50–75% of infected cases are asymptomatic and are left untreated. *M. genitalium* has lately been discovered to impair fertility, but the role of other mycoplasmas and viruses is less well-known.

It is possible to reduce the infertility rate due to sexually transmitted infections by routine screening of high-risk populations, treating the asymptomatic cases and imparting sex education. The development of a vaccine may be considered as the best option to prevent chlamydial infection-related infertility, but still needs a lot of research.

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# 94

## Aging, Sexual Behavior, and HIV/STI Risk

Massimo Giuliani

*The worst thing about aging is that you stay young.*  
— J Cocteau, 1958

### Introduction

Aging is generally associated with a decrease in sexual arousal and activity, and studies have shown that the frequency of sexual intercourse decreases with age in both the genders, particularly as a result of physiological changes, as opposed to changes in satisfaction or desire.<sup>1</sup> Indeed, sexual desire continues well into later life for both men and women but can be limited by aging in various ways.

In general, the effect of aging on sexual performance depends upon the physical and mental health of the individual.<sup>2</sup> Nevertheless, many authors agree that the physical changes that occur in older age can modify sexual experiences but do not completely extinguish them.<sup>3,4</sup> The main factors that contribute to a decrease in sexual activity among older individuals are: medication, disease states, physical barriers, negative perception of body image, mental disorders,<sup>5</sup> and some important physiological changes. The main described physiological changes which reduce the sexual performance of the older persons include: the alteration in the vaginal secretions and flattening of the vaginal epithelium in women and erectile dysfunctions in men, whereas other factors do not seem to greatly limit sexual intercourse (Table 94.1).<sup>6,7</sup>

In recent years, sexuality in older groups has solicited the interest of public-health authorities in industrialized countries because of a sudden increase in the incidence of sexually transmitted infections (STI) among persons over 50 and 60 years of age. Despite the fact that aging is usually associated with a decrease in sexual arousal and activity, in recent decades some factors have enhanced the sexual life of individuals in their sixties, seventies, and even eighties. This may have increased the proportion of individuals in mid-life and late adulthood who engage in sexual behavior at-risk for HIV infection and other STIs.

Within the proactive factors currently associated with an extension of sexual activities into late ages (Table 94.2), nowadays, the greatest role seems to be played by the availability of drugs to

enhance sexual performance and the increased social acceptability of sexually active elderly persons.

An extensive survey conducted in Sweden over the past 30 years has shown that the self-reported quantity and quality of sexual experiences among 70-year-olds have improved in recent decades. Men and women from later birth cohorts reported higher satisfaction with sexuality, fewer sexual dysfunctions, and more positive sexual attitudes and practices in later life than those from earlier birth cohorts.<sup>8</sup>

**Table 94.1:** Biological and Physiological Changes Associated with Modifications of Sexual Performance among Older Individuals

	Male	Female
Testosterone level decrease	Yes	Yes
Estrogens level decrease	–	Yes
Desire decrease	Yes	Yes
Penile sensitivity decrease	Yes	–
Penile rigidity decrease	Yes	–
Reduction of vaginal secretions	–	Yes
Reduction of the period of inevitability before ejaculation	Yes	–
Reduction of semen volume per ejaculation	Yes	–
Refractory period extension	Yes	No
Reduction of pre-ejaculatory liquid	Yes	–
Reduction of nocturnal spontaneous erection	Yes	–

**Table 94.2:** Selected Proactive Factors Associated with Sexual Activity in Late Ages

- Extension of life expectancy
- Increased healthy survival
- Improved quality of life and physical and psychological well-being
- Lower impact of drugs for unrelated disorders on sexual performance
- Availability of drugs against sexual dysfunctions
- Improved social acceptability of sexuality in later-life

## Prevalence of Sexual Activity in Older People

Whereas there is extensive literature on the sexuality of adults and young persons, studies on the characteristics and nature of sexuality in older age groups are lacking. Nevertheless, the importance of better understanding the complexity and determinants of the human behaviors associated with the diseases with major impact on the western health systems, stresses the need for extensive investigations to identify the characteristics of sexual behavior along all ages.

Several studies seem to confirm that a high proportion of men and women remain sexually active well into later life. In particular, behavioral studies on sexuality among older adults in Western countries have shown that, although many elderly persons are sexually active over 60 and 70 years of age, in general, older women are less likely to have an intimate relationship and engage in sexual activities than men. Pfeiffer et al. reported that 95% of men aged 46–50 and 28% of men aged 66–71 have sexual intercourse on a weekly basis.<sup>9</sup> Diokno et al. reported that nearly 74% of married men older than 60 remain sexually active.<sup>10</sup> A 1988 study about sexual interest and behavior showed that 62% of men and 30% of women aged 80–102 were still having sex.<sup>11</sup> Recently, Smith et al. reported that, among a small sample of individuals over 70 years of age residing in New York, 18% of women and 41% of men were sexually active.<sup>12</sup>

An additional recent study conducted on a large sample ( $n = 3005$ ) of community-dwelling persons from 57 to 85 years of age, interviewed during the second semester of 2005 and the first quarter of 2006, showed a steady decrease in the prevalence of sexual activity with age and a positive association with self-reported health. However, among the sexually active responders, 67% of those aged 65 to 74 years and the 38.5% of those over 74 years, reported having had sex in the previous year.<sup>13</sup>

Johnson et al. reported that the frequency of sexual intercourses is strongly associated with *having a partner* and is highest among married or cohabiting people. Moreover, 54% of the sexually active men aged 75–85 years reported the use of medication to improve sexual performance.<sup>14</sup>

Some studies have shown that an adult's sexual expression is not age dependent<sup>15</sup> but older individuals are commonly more reluctant than younger ones to talk about sexuality. Moreover, some individuals might be influenced by the cultural context and social acceptability in the community where their sexuality was developed and sexual activity started. By way of example, many older homosexual men have started to engage in sex when having sex with men was socially unacceptable and in some countries also illegal, so that they have learnt to mask their sexual habits.

## Aging, Gender, and Risk of STIs

In general, data from observational studies seem to confirm that among the elderly important differences in sexual risk behavior exist between men and women.<sup>16</sup> Older men have been found to be at greater risk for STIs than older women because of: (i) a

larger number of recent sexual partners; (ii) a disproportionately greater access to sex for money; (iii) sex with a same-sex partner; (iv) greater frequency of sex overseas or with a non-national partner; and (v) the existence of drugs for counteracting the physiological changes associated with a reduction in sexual activity.<sup>17</sup> Moreover, among older men who have sex with men, although the frequency of sex decreases with age, some studies have reported a progressive increase in the frequency of at-risk practices, such as unprotected receptive anal and oral intercourse due to impairment associated with physical and physiological changes (e.g., loss of bodily strength, erectile dysfunction, genital sensitivity decrease). Focus groups conducted with over forty Canadian gays and bisexual men, showed that some age-related issues have an impact on safer sex decision-making even before the age of 50 years. If the decreased attractiveness, widowerhood, the loss of support network from AIDS seem to protect from the risky sex, contrarily, condom fatigue, treatment optimism, inserter invulnerability, depression, and the negative effects of condom-use in keeping erections seem to support the engagement in risky situations.<sup>18,19</sup>

Older women tend to be at risk for STIs because they are less likely to engage in protected sexual intercourse, with respect to same-age men. In Australia, among 1976 men and 462 women over 50 years of age, the proportion of sexually active persons who had used condoms in the preceding 3 months was 54% among men and 19% among women ( $\chi^2 = 63.3$ ,  $p < 0.05$ ).<sup>17</sup>

Some authors have reported that older women are increasingly at risk of STIs during the peri- and postmenopausal period. In this period, STI-related genital symptoms are often nonspecific or absent or may be misclassified as being due to the specific hormonal state. Furthermore, women in this period may not be aware of the risk of infection, with consequent delayed or missed STI diagnosis.<sup>20</sup>

In the United States, among the more than 3200 adults over 50 years of age interviewed in the National AIDS Behavioural Study (NABS) from 1993 to 1994, 7.0% had taken a risk for HIV/STI during the previous year, 83.0% had not used a condom during sex, and 80.0% were not tested for HIV.<sup>21</sup> Moreover, of the 2058 individuals who reported more than two sexual partners in the preceding 5 years, 10.0% were 50–59 years old, 9.0% were 60–69 years old, and 8.0% were over 70 years.<sup>22</sup>

## STIs among Elderly

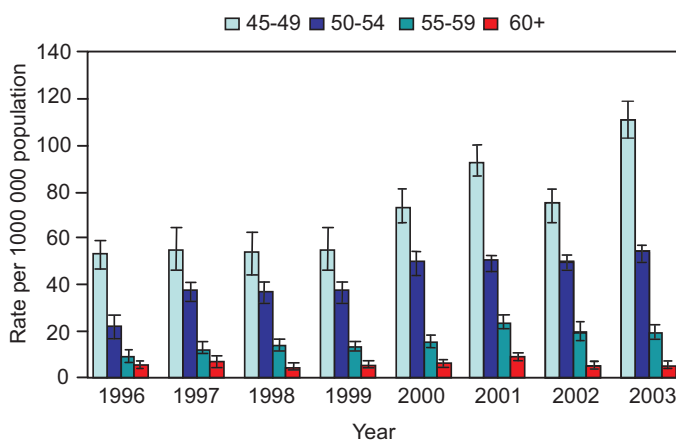
Since the year 2000, in the industrialized countries sexual behavior has again started to represent an important determinant of morbidity and use of healthcare services in all age groups. A dramatic increase in the incidence of unplanned pregnancies and abortions among adolescents and young adults and a dramatic re-emergence of STIs both in the general population and vulnerable groups, such as MSM and migrants, have been observed.<sup>23–25</sup> Moreover, in Western countries some behavioral studies have shown that millions of men and women over 50 and 60 years engage in sexual behavior at-risk for HIV and other STIs. However, recent data on STIs among older persons are poorly available, and comparable studies and information

on the circulation of STIs within this population group are yet scarce. Nevertheless, data provided by surveillance systems and local surveys conducted in several developed countries since 2000 seem to suggest a progressive increase in the number of older individuals with a new episode of STI among attendees of clinical centers. Generally, in the field of STIs, the term “older patient” refers to persons 50 years of age or older, though in some studies it refers to lower ages.

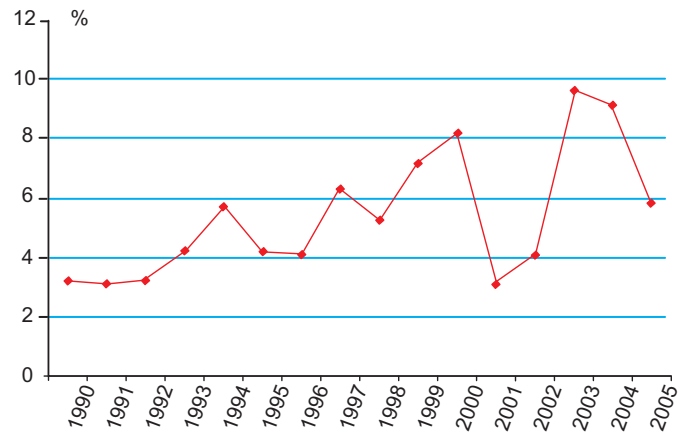
Some accurate information on STIs among older individuals has been provided by ongoing National STI Surveillance Systems in several developed countries. For example, in the United Kingdom, from 1996 to 2003, the proportion of STIs other than HIV infection among the total reported cases in individuals over 45 years of age increased from 3.7% to 4.3% and the incidence rate of STIs in this age group more than doubled in 2003 compared to 1996. Moreover, for the major STIs this increase has been observed in all age groups over 45 and particularly in individuals aged 55–59 years (Fig. 94.1).<sup>26</sup> A previous study from the United Kingdom had shown that around 8.0% of the new or rebooked patients in a genitourinary medicine clinic in Portsmouth were aged 50 years or older (median 57 years).<sup>27</sup> In the United States, data from Washington State’s STI Surveillance showed that between 1992 and 1998, 1.3% of the cases had been diagnosed among individuals 50–80 years old and that the most common STIs were nongonococcal urethritis in men and genital herpes in women. In this study, older patients were more likely than younger persons to be white, to seek care at private facilities, and to be symptomatic at the clinical consultation.<sup>28</sup>

Among the attendees at a sexual health clinic in Sydney from 1993 to 2003, 40.0% showed genital symptoms, 23.0% and 13.0% requested STI testing and HIV-1 testing/care, respectively. The most common STIs were genital herpes (10.0% women, 6.0% men) and nongonococcal infections (9.0% in both genders).<sup>17</sup>

In Italy, according to data from the STI National Sentinel Surveillance System, around 10.0% of all reported cases have



**Fig. 94.1:** Rates (95% CI) of selected sexually transmitted infections in people aged >44 years in the West Midlands, UK, by year of diagnosis and age group: 1996–2003 (Modified from Bodley-Tickell AT, et al. 2008).



**Fig. 94.2:** Trend of prevalence of HIV-1 infection among 5256 Italian STI patients over 50 years of age, by year; Italy, STI Surveillance System, 1990–2005.

**Table 94.3:** Factors Associated with the Increased Risk of STIs among the Older Individuals

- Lack of information and attitudes about STI prevention
- Changes in social patterns and relationships (single, divorced, separated, or widowed)
- Availability of effective medication against erectile dysfunction
- Improved accessibility to sex for money

been diagnosed in individuals over 50 years of age. From 1991 to 2006, 9845 new cases of STIs were reported in this age group. The median age was 56.7 years (IQR= 53–64 yrs) and the male-to-female ratio was 2:1, higher than that observed in other younger age groups. The most common STIs reported in persons over 50 years were genital herpes and genital warts among men, and unspecified vaginal infections and latent syphilis among women.<sup>29</sup> Moreover, in this population the cumulative prevalence of HIV-1 infection was 5.0% and the trend has shown a progressive increase, particularly after 1995 (Fig. 94.2).

In developed countries, the observed increase in STI incidence among the elderly seems to be associated with specific social and behavioral factors. Data from a behavioral study have shown that these factors range from lack of information and skills to changes in the individual and the social status (Table 94.3).<sup>30</sup>

### Preventative Attitudes among Elderly

The elderly, compared to younger individuals, seem to be less likely to use condoms during sex or to have been tested for HIV. Moreover, in developed countries, older adults generally know less about HIV infection and AIDS than younger people, including how the disease is transmitted.

Older people have been neglected by health educators, overlooked by health workers, and might be excluded from HIV facilities and prevention programs.

Several factors seem to affect the communication between elderly persons and health specialists about sex education and information. Moreover, it is not easy for general practitioners



**Table 94.4:** Reasons Associated with the Lack of Investigation of Sexual Behavior in the Older Individuals

- Sexual history is not included in current anamnesis taken in older patients
- Elderly are not perceived by the physician to be a sexual risk taker
- Reluctance in elderly to disclose sexual health concerns
- Fear and embarrassment
- Lower accessibility to clinical centers

to talk about sex with their patients, often because of a lack of communication skills, which also limits the evaluation of symptoms associated with STIs (Table 94.4).

Moreover, older persons seem to be excluded from the target populations identified for prevention campaigns. Some authors recommended that older people should be encouraged to attend STI facilities by improving accessibility and welcoming them.<sup>31</sup> This is an important public-health goal, particularly today, when sexual activity after the reproductive years is made easier by hormone replacement therapy for women and erectile dysfunction treatment for men.

## Elderly and HIV Infection

Until a few years ago, it was uncommon to read about a case of a new HIV infection in an elderly man, and the cases that did exist were described as anecdotal case reports.<sup>32</sup> However, in the past decade the size of the aged population living with HIV/AIDS has progressively increased worldwide, and the World Health Organization estimates that there are approximately 3 million individuals over 50 years of age living with HIV/AIDS.<sup>33</sup> By 2015, it is expected that around 50% of HIV-infected persons will be older than 50 years.

In Western countries, this progressive aging of the AIDS epidemic has been observed since 2000, also because of some important clinical and epidemiologic changes. The main factors are:

- (a) the introduction of highly activity antiretroviral therapy (HAART) in the mid-1990s and the consequent increase in the survival of persons with HIV infection;
- (b) the tendency of older HIV-infected individuals to transmit the infection mainly to age-peer sexual partners;
- (c) the tendency of HIV-infected individuals who minimize their own sexual risk to be diagnosed late, at an older age; and
- (d) an increase in the number of persons, particularly men, who acquired HIV infection in older age during a prolonged drug-supported sexual activity.

Early in the AIDS epidemic, older persons represented a large proportion of the persons infected through blood products or transfusions, yet this proportion has greatly decreased since the introduction of policies for reducing the risks related to transfusions, especially in Western countries.

In a seroprevalence study conducted in the pre-HAART era among hospital patients over 60 years of age and dead for causes

not related to HIV/AIDS, 6.2% of men and 8.9% of women were HIV-infected, and over 60.0% of these individuals had no identifiable risk factors for HIV infection.<sup>34</sup> Also today, HIV infection in the elderly may remain misclassified until a late diagnosis or unrecognized until the death from other co-causes. In all countries it is very common for healthcare workers to neglect to screen older individuals for HIV. The difficulties in talking about sexuality or occasional sex by the physician with the elderly may lead to false assumptions about risk behavior and to also limit HIV screening. Today, in the United States, according to the recently revised guidelines for routine HIV testing, all adults over 50 years old must be subjected to HIV testing, regardless of risk,<sup>35</sup> and some authors have also recently determined that one time HIV testing is cost-effective in sexually active people over the age of 65 years.<sup>36</sup>

In the United States, AIDS patients older than 50 years represented more than 12.0% of the total reported diagnoses from 1982 to 2007. In 2007 this proportion increased to 17.0% (13% represented by 50 to 59-year-olds and 4.0% by persons over 60 years), and is expected to continue to increase over the next decade.<sup>37</sup>

In Canada, as of December 2006, 8.0% of the new HIV cases and 12.0% of AIDS patients were 50 years of age or older.<sup>38</sup> In Australia, 14.0% of AIDS cases and 17.0% of deaths due to AIDS notified until December 2007 were observed in people over the age of 50 years.<sup>39</sup>

A similar trend has been observed in Europe, where nearly 17% of the persons with AIDS diagnosed between 2001 and 2005 were older than 50 years. The proportion of new HIV diagnoses in this age group has greatly increased, reaching 15.6% in 2006.<sup>40</sup>

In the United Kingdom, in 2007, 8.5% of new HIV infections were diagnosed in men over 50 and nearly 4% in women in the same age group.<sup>41</sup>

In Italy, according to data from AIDS surveillance system, from 1982 to 2005, 8.8% of the notified cases were observed among persons over 50 years of age, and this proportion has increased over time, from 4.9% in 1982–1990 to 15.9% in 2000–2005. Among older Italian AIDS patients there is a higher proportion of cases due to sexual transmission, than among younger patients.<sup>42</sup> In a study from Italy between January 2004 and March 2007 among individuals over 50 years of age with a new HIV diagnosis, higher proportion of them were in a more advanced stage of HIV infection. Majority of them reported heterosexual exposure and were never tested for HIV before.<sup>43</sup>

Since the beginning of the AIDS epidemic, older persons with HIV have had a higher morbidity, higher fatality rates, and a shorter AIDS-free survival than adults and young persons. Before the introduction of HAART, large multicenter studies showed that from 13.0% to 14.0% of HIV-infected individuals over 50 years of age died within 1 month of the AIDS diagnosis, twice the proportion observed in persons aged 13–49 years (6.0%).<sup>44,45</sup> This difference was largely explained by late diagnosis and comorbidity, though a weaker immunological response in terms of CD4+ cell reconstitution also seems to have played a

**Table 94.5:** Major Clinical Characteristics of Older (Age >50 years) Versus Younger HIV-infected Individuals

- Decreased interval between HIV and AIDS diagnoses
- Higher rates of concurrent illness (comorbidity)
- Increased mortality rates
- Faster viral suppression during HAART
- Higher rates of adherence to HAART
- Slower CD4+ cell count positive slope during HAART
- Increased risk of severe adverse events associated with HAART
- Increased risk of CNS HIV-associated illness (Encephalopathy, ADC, cognitive impairment)

CNS, central nervous system; HAART: highly active antiretroviral therapy; ADC: AIDS dementia complex.

role. The main differences between older and younger persons with HIV, in terms of HIV disease presentation and course, are listed in Table 94.5.

## Aging and HIV Disease

Many years ago, Italian researchers established in a longitudinal study that the natural course of HIV disease is modified by the increasing age at the diagnosis (Fig. 94.3), also as a result of basically immunological changes that are naturally associated with aging.<sup>46</sup>

In healthy older persons, a natural involution of the thymus occurs and the thymic volume is significantly lower in persons 50 years of age and older than younger individuals.<sup>47</sup> The production of naïve T cells also tends to decline with age; thymic output is minimal after the age of 55 years,<sup>48</sup> and the populations of memory T cell and functioning CD8+ cytotoxic cells are significantly reduced.<sup>49</sup> Thymic function and production of naïve T cells may be altered and inhibited during HIV disease.<sup>50</sup> For these biological and immunological differences, the progression of HIV infection in the elderly may be faster than among younger persons.

Many studies have suggested that older patients may not respond as well to HAART as younger patients; particularly, the risk of clinical progression to AIDS has been reported to be 1.5 times higher and the immune restoration in terms of positive recovery of CD4+ cells may be lower despite a faster virological

success.<sup>51</sup> That older patients are more likely than younger patients to achieve HIV-1 RNA levels lower than 500 copies/mL was confirmed in a large cohort study that compared immunological and virological responses to, and tolerability for HAART in 997 patients, 50 years of age or older and 4093 younger patients. The study showed that the virological success in the older patients was sustained by a better adherence to HAART, despite a higher risk of adverse events, such as metabolic, hematologic, and renal abnormalities.<sup>52</sup>

Older patients may be more likely than younger patients to develop significant toxicities, including dyslipidemia, impaired glucose metabolism, pancreatitis, neuropathy, hepatotoxicity, and lactic acidosis because older people are more likely to have comorbidities, including cardiovascular disease, renal disease, diabetes, bone loss, and obesity, which complicate the use of antiretroviral therapy. Thus a balance must be found between the need to treat older individuals earlier, so as to sustain immune function, and the potentially greater risk of cumulative toxicity from HAART.

The nature of AIDS-defining diseases also differs between older and younger individuals. Upon AIDS diagnosis, older adults have a higher risk of developing HIV encephalopathy or wasting syndrome and of presenting multiple AIDS-defining events than younger adults.<sup>42,53</sup> Grabar et al. have also shown that among older patients, there is a higher risk of HIV encephalopathy (HR=2.8), CMV disease (HR=5.0), and Kaposi's sarcoma (HR=3.0) compared to younger patients.<sup>51</sup>

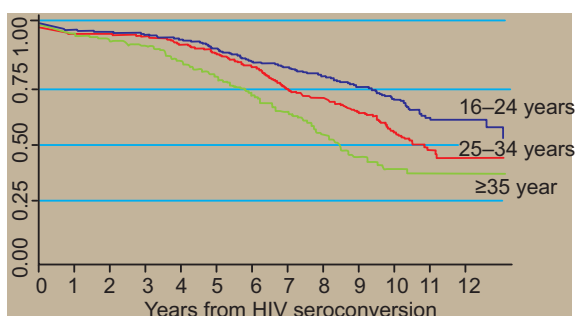
Today, as the HIV-population ages, non-AIDS defining cancers are becoming a major concern. An increased incidence of liver, lung, anal, skin as well as hematopoietic cancers was observed, as a result of the association of other risk factors (i.e., smoking, sun, HPV infection) and the HIV-induced immune dysregulation.<sup>54</sup> This fact stresses the need to include in the follow-up of the older HIV patients, the management of their age-associated cancer risk by targeted oncological screening procedures and educational programs particularly aimed at cessation of smoking, reduction of sun exposure, and dietary protein intake.

## Conclusions

Today there exists much evidence of the role of sexual behavior as a determinant of sexually acquired disease and associated disability in the aged populations in developed countries. The recent emergence of STIs and HIV infection in older populations represents a measurable biological marker of at-risk sexual activity for a large proportion of aged individuals. Additional studies are needed to better explain the link between sexual activity in late ages and the risk of STI/HIV, also to enhance the effectiveness of preventive programs toward this growing population.

Counseling activities and screening programs for STIs and HIV infection must also be tailored for older persons, and their accessibility to STI clinics must be enhanced, particularly to reduce delays in diagnosis and improve the efficacy of treatments.

Today it is also clear that the risk of progressive enlargement of HIV epidemic is associated with unsafe sex by infected individuals



**Fig. 94.3:** Kaplan-Meier cumulative survival rate according to age group by age at seroconversion (Modified from Pezzotti et al. 1992).

and the fact that these individuals are older than the susceptible partner stresses the need to continuously improve preventative information, attitudes, and practices in this population.<sup>55</sup> Failure to consider HIV infection in older patients also contributes to the greater risk of older HIV-infected to present with an advanced disease at the diagnosis.

Moreover, the barriers to effective communication between older patients and physicians or other health caregivers about sexual behavior should be removed, to also better manage STI risk and occult HIV infection.

To date, no guidelines are available that specifically address the needs of an elderly STI/HIV-infected patient. Also for this reason, the pre-existing comorbidity and the increased susceptibility of older individuals to drug toxicity, stresses the need to improve their attitudes towards condom use and their perception of risks associated with sexual activity in order to prevent acquisition of any STI or HIV-1 infection.

### Summary

In recent decades, some factors have enhanced the sexual life of individuals in their sixties, seventies, and even eighties. Worldwide, this fact has growing the population of individuals in midlife and late adulthood who engage in sexual behaviour at-risk for HIV infection and other sexually transmitted infections (STI). In this chapter, selected studies are reviewed to disentangle the relationships among old age, sexuality, and infections. The different sections are focused from the biological and physiological changes observed in the sexual performances in old ages to the epidemiology and the clinical aspects of STI and HIV infection in elderly. Also some final suggestions are summarized to enhance the preventative pressure of the educational programmes targeted at this population.

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# Sexually Transmitted Infections in the Female Sex Worker Community

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# 95

## Introduction

Our present understanding of 'sex work' includes male, female, and transgender sex workers. While the problems/issues in meeting the sexual health needs of all such workers hold equal importance, this chapter will deal only with female sex workers. However, most of the principles on which it is based are equally applicable to other groups of sex workers.

In the recent past, the issue of the management of sexually transmitted infections (STIs) among sex workers has assumed increasing importance because of the focus on HIV/AIDS prevention and care. There is a strong correlation between HIV and STI transmission. The presence of STIs in one partner facilitates both sexual transmission and acquisition of HIV. Preventive policies and principles including various tools that are applicable to STIs also hold good for HIV. HIV prevalence among the population of female sex workers in different cities across the world is found to be high.<sup>1</sup> STI prevalence rates in the Asia region continue to be high among sex workers. Studies conducted during 2000 in seven sites in India found seroprevalence of syphilis among sex workers to be ranging between 7% and 56%<sup>2</sup>; gonorrhea prevalence was found to be 36% among street-based sex workers in Dhaka, Bangladesh compared to only 0.5% among women attending health services.<sup>3-4</sup> Sex workers surveyed in 10 Indonesian cities during the year 2005 showed that 50% of them are infected with one or more curable STIs.<sup>5</sup> Comparable rates have been reported throughout the region, where HIV prevalence is consistently higher among sex workers—female, male, and transgender—than among other populations.<sup>6,7-11</sup> Yet, despite these high rates, only 20% of sex workers are currently estimated to have access to basic prevention services.<sup>12</sup>

Making good quality STI care and services available and accessible to sex workers could effectively slow down the transmission of HIV.

## Significance of STI Management in Sex Worker Communities

Even though the comparative size of the sex worker population in any given situation/country is small in relation to that of

the general population, special emphasis on the management of individual cases of STI as well as on the development of an effective STI management system is important because:

- Sex workers constitute the core group of transmitters of infection to the general population.
- Their work and social status places them at an increased risk of contracting infection from multiple partners.
- As sex work is an economic activity, the disease burden has a direct impact on their capacity to earn a livelihood and support themselves and their families.
- Effective STI prevention and care program has direct implications in the transmission of HIV/AIDS.

## Theoretical Construct

The classical medical model of disease management is based on a hypothesis that considers a linear relationship between the agent and the host. This model ignores all social and environmental factors that impinge upon the process of disease transmission, progression, and management. Although the limitations of this model are well-understood and documented in recent times, practices still remain unchanged. This is partly because the tremendous advances in the branch of curative medicine in the fifties and sixties dazzled the world and great emphasis and hope was thereby placed on disease control through individualized treatment and care, ignoring all other environmental and social factors.

Secondly, there are few well-accepted and articulated models of prevention and management that take account of social and environmental factors for diseases. The most effective approach is to view STI as an occupational disease and program planning should follow the basic policies and guidelines of workplace safety. This approach brings into focus all possible issues related to workplace environment, which directly or indirectly influence the health and well-being of workers engaged in the sex industry. This includes:

- Contractual agreements related to the work; involvement of other agencies such as law enforcing authorities, the municipal corporation, the department of social welfare, landlords, etc.; the recruitment of workers, stipulation of the minimum age, hours of

work and work conditions; a safe and secure work environment, and the provision of basic amenities, e.g., water and sanitation. In legalized brothels in Netherlands and Australia, brothel owners are compelled to follow the standard norms in providing safety and security and health services to individual sex workers in accordance with the laws and policies of the Government. Adequate compliance is assured through a system of supervision and monitoring and regular inspection.<sup>13</sup>

- The principles of the management of workplace safety followed in other settings usually emphasize the active participation of workers. The management and workers through state-mitigated policies and strategies jointly decide upon workplace safety standards and practices. Both workers and management are then obliged to follow them. Globally, experience shows that the participation of workers ensures an improvement in the quality of the safety of the workplace as well as that of the programs and services designed to improve health and safety. The experience in Sonagachi, Kolkata (India) and Tangail (Bangladesh) also demonstrates the effectiveness of sex workers' participation in ensuring workplace safety.<sup>14</sup>
- In occupational health programs, preventive and curative services are customarily integrated. This has special implications for the prevention of STIs especially among sex workers, as unless consistent condom use for prevention is ensured, the cycle of infection and reinfection cannot be broken.

## A Model for Comprehensive Management of STIs in Sex Workers

Planning and managing an effective STI service delivery program requires sufficient attention that to be paid not only to the biomedical and epidemiological aspects of disease transmission and progression, but also to important sociopolitical factors that influence outcome. Over the last decade, there has been considerable development in the areas of laboratory-based STI diagnoses and simplification of treatment modalities for many STIs. In the recent past, the use and application of point of care testing,<sup>15</sup> which provides immediate and accurate diagnoses, is getting importance. The single dose treatments for many STIs have improved the outcome of STI management. While there have been substantial developments in the biomedical field, and proven treatment regimens are well-established, the greater challenges still remain in developing effective and appropriate nonjudgmental services that adequately address the special conditions of marginal and stigmatized populations like female sex workers. Development of an effective and comprehensive STI management program among the sex workers calls for articulation of an appropriate strategy that needs to be based on community friendly guidelines and approaches.

### COMMUNITY LED STI MANAGEMENT APPROACHES

To improve both the quality and coverage of STI management services one needs to move beyond the traditional approaches to STI management – what restricts STI service development within

the four walls of the clinical medicine (e.g., doctor, medicine, and prescription). Social approaches to STI management have opened up new avenue to engage and involve service recipient as 'provider' and co-owner of service delivery system. Community led STI management approaches can be articulated under four 'D's' (destigmatization, demystification, deconstruction, and democratization).<sup>16</sup>

## Destigmatization of Sex, Sex Work, and Sexually Transmitted Infections

One of the primary reason behind improper and under utilization of STI services is linked to the shame and stigma attached to it. To begin with it can be addressed by the outreach and peer worker through introduction of human anatomy and physiology as part of health communication strategy. Sex workers should feel comfortable in observing and examining their own body including genital parts and develop a healthy and nonjudgmental attitude towards sex organ irrespective of her occupation. Outreach workers including peers should share with the community members appropriate knowledge and information about hygienic practices; in addition to that they should encourage sex workers to identify any painless ulcer in the genital part and report to attending doctors in the clinics which would help identifying nonsymptomatic cases including its timely intervention and treatment. This has immense importance in influencing the overall treatment seeking behavior of sex worker. All staff members of the program including peers and outreach worker must not view sex as a 'sinful act' and garner adequate confidence to discuss and deal with issues related to sex and sexually transmitted diseases (STDs).

## Demystification of the Technical Aspects of STD Services

In addition to fear and stigma attached to sex and sex work there is one more issue. In our society anything related to sex is shrouded with mysticism and STI disease is no exception. A section of self professed nonqualified sexologist has augmented this phenomenon through their day to day practices. So a conscious effort has to be made by the program implementers to demystify STI management services. Community members should be allowed to develop their knowledge, skill, and aptitude to know and learn about the science of sex and sexually transmitted illnesses including STI management related issues and challenges. Right from the beginning program implements must involve selected number of peer workers in the STI management team, with a view to built their capacity. They can be trained to deal with history taking, maintenance of outdoor registers in addition to follow-up of cases. They need to comprehend basics of lab techniques and procedures. All these efforts enable community members to play their role not just as recipient of services but an able member of the community to help improving treatment seeking behavior of the sex worker through sharing information, counseling, and follow-up of cases. This sort of activities help



demystifying STI management services and help staff members and consumer of services to develop a healthy attitude towards sex and sexually transmitted diseases.

## Deconstruction of STI Management Services

Both outreach and medical personnel working in the clinic jointly develop STI services. Essentially, it is the peer workers who motivate community members to access STI services. They counsel patients to ensure adherence to treatment, encourage for regular use of condom, and facilitate partner's treatment. All these in combination constitute STD management. Partner's treatment, the most difficult component of the STI management services can be improved to a large extent through delegating responsibility to the outreach team, who could influence the sex workers to encourage and bring her partner for availing STI treatment. Development and delivery of different elements of STI services are made through the engagement of a group of professionals and community members ranging from doctors, peers, counselors, and outreach workers. All of them are not placed in the clinic, neither they perform their respective role sitting in one place. However, all members share specific role and responsibilities in creating and delivering STI services. This comprehension helps deconstructing STI management mechanism including its delivery.

## Democratization of STI Management Services (Issues of Governance)

Accessibility and utilization of STI services by the sex worker depends on varieties of internal and external factors which includes development of service delivery mechanism including its approaches. Improvement of quality of STI management services cannot be made possible without having an effective coordinating mechanism between the members of STI management team. The program planner needs to develop adequate system to help share and reflect on clinic based output with the inputs of the outreach team and their findings. Both categories of staff members should share a common platform in terms of their rights and shared responsibilities. It needs to be reflected both in monitoring as well as in the evaluation system of the STI services. (This has been amply explained in clinical governance and audit section.) Regular meeting and sharing of information has to be organized in between outreach and clinical team to improve the quality of services including midterm correction. An open transparent and formal communication channel is required to ensure regular feedback, analysis of data, presentation of cases, etc. to keep track on quality and effectiveness of the ongoing STD management program and its impact on the community.

Designing a model for comprehensive management of STI in sex worker community should address the following challenges.

### Reaching Out to the Community

By and large, in most countries sex work is seen as an illegal trade. In order to protect itself, the trade stays "hidden". This

makes it very difficult to identify and reach out to its members. Some countries have sought to identify sex workers through a system of "registration" of either brothel or sex workers. This has its own limitations, as it creates a distinction between "officially recognized" sex workers for whom there may be some services, and those not recognized will still fall outside the safety net of services. New strategies are required that will reach out to all sex workers, based not on registration but on the right to services and well-being, and which will encourage their participation.

Moreover, as sex work is considered immoral, mainstream society pretends that this trade does not exist and turns a blind eye to it, ignoring it in many ways including the provision of services. In many country-settings, laws and rules are framed such that they criminalize not only sex work but also the entire environment around it.<sup>16,17</sup> All these factors, in combination, make reaching sex workers a formidable challenge. In many countries, although sex work is not illegal, laws are ambiguous, and their interpretation is left to the law enforcers such as policemen and local goons.

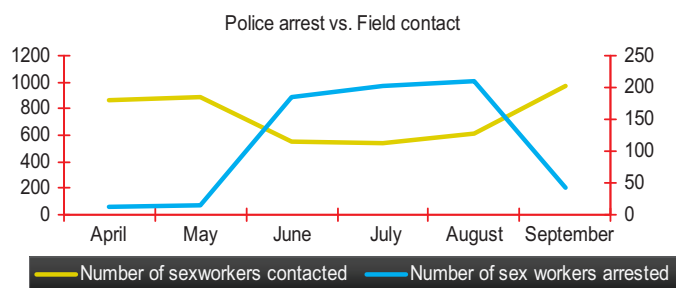
Levels of social tolerance and existing legal tools influence the structure of sex trade in different settings, e.g., whether it is recognized, whether brothels are registered or not, whether sex work is practiced as residence-based, hotel-based, street-based, or disguised as massage parlors, escort services, etc. In the recent past the use of mobile phone has become the most preferred channel of communication through which sex worker or clients fix appointments and clients pick up sex workers from the designated sites making it more difficult to reach out to them.

Factors that determine the structure and functioning of sex trade predominantly control sexual practices. So it is of paramount importance to focus on all these interdependent structural factors while developing STI prevention and control program and its strategies.

### Making Services Accessible

There are several barriers that sex workers face in attempting to access STI treatment. These ranges from lack of information and the necessary familiarity to use a service, mobility, distance, purchasing power, location of clinics, and timing of services. The barriers are not only physical but include the strict control imposed by the sex trade controller. For example, the madams or owners of the brothel/hotel strictly limit the mobility of sex workers and do not allow them to go out. Frequent police raids further restrict their movement. Graph presented in Figure 95.1 shows how police raids made it difficult for peer educators to reach out to sex workers vis-à-vis the use of condom and other preventive or care related services.

Local goons can impose their own modalities, including restrictions on where the women can go, and for what reasons. In order to maintain total control these manipulators do not allow the women to mix with others who may provide them information and access to the external world.



**Fig. 95.1:** Graph—police arrest vs. field contact. *Source:* Presentation by Ashodaya Samithi (Mysore) at the National Consultation held at Delhi, November 2007.

### Making Services Acceptable

The availability of a medically sound service is not enough to promote its use by sex workers. A positive attempt has to be made to make it acceptable. An acceptable service is one where the special needs of sex workers are respected.

The service must uphold the dignity and respect of the patient. A sex worker attending a service does so as a patient, not as a sex worker. Yet, often she is treated with stigma and discrimination; staff is disrespectful and makes comments that are highly inappropriate in a healthcare setting, with references made to her occupation and her behavior. All these serve as deterrents to seek treatment and pose barriers to full and effective STI management.

Like any other person, sex workers require privacy and confidentiality in seeking STI services. In their case, the breach of confidentiality can seriously impair their ability to draw clients and earn their livelihood.

### Creating Enabling Environment

Sex work is an occupation for a certain group of women, who maintain their livelihood through this activity. Considering this activity as an occupation broadens the scope of prevention and treatment programs to extend beyond individual medical treatment and take account of determinants that usually lie beyond the purview of medical treatment. This includes environmental factors, which influence or control the sex occupation, trade, and practices in a given context. The laws related to sex trade, the way society views sex, sexuality, and sex work also determine an individual's ability to protect oneself, prevent infection, or use treatment services.<sup>17,18</sup> Other environmental factors that increase risk and violence in the brothel or in the street from hooligans and the police. The high mobility of sex workers is an important barrier making completion of treatment a difficult proposition. Attempts by a section of civil society organizations including government department to enforce rehabilitation program for sex workers against their will poses difficulties in carrying out effective STI intervention program both in brothel as well as in street settings. So there is a need to create a supportive environment for the sex workers so that they feel comfortable to

access services without any fear and apprehension. Program has to incorporate appropriate advocacy element with the police and the administration as part of building supportive environment for the communities. Indian National AIDS Control Program (NACP) with a view to enhance target communities' access and utilization to HIV/STI prevention and care services introduced the concept of 'creating enabling environment' as an integral component of intervention program during the 2nd phase of intervention (2000–2005) and strengthened it further in its 3rd phase spreading from 2005 to 2012 through providing appropriate budgetary allocation to carry out advocacy related activities, with various stakeholders including police and administration. In addition to that National Program added another component to enable and empower communities so that they can access and utilize all relevant preventive and care services including STI services. Indian National Program has fixed a target to reach out to 1.2 million female sex workers with quality HIV and STI services and making it accessible, acceptable, and utilizable by the community member to stall the HIV epidemic in the country.<sup>19</sup>

### Marginal Status

Forced to live on the margins of society and often denied access to basic services, sex workers have very little access to the common pool of information and social services, including health services that the general population can use. This is a great paradox, as the sex workers, as mentioned earlier, require information and services more than the rest of the population. Attempts to bring them into contact with and to make them use the existing services hardly work due to various sociocultural factors besides resistance and discriminatory practices often meted out by the mainstream society and service providers. Hence, it is important to develop specially designed delivery systems looking from the perspective and the social position of the community.

### Stigma

Most societies attach stigma to sex and sexuality, and this stigma is transferred onto all activities associated with sex, other than procreation. The stigma is most pronounced when sex is exchanged for money, involves multiple partners, and is seen as a threat to social and family stability. Sex work then meets all possible criteria for stigmatization.

As a result of this stigma, sex workers are in effect denied even a range of basic services, including sanitation and water supply. Further, the usual attempts to regulate the conditions of work, labor and its environment, now well-established and accepted in most work situations, are not usually applied to sex work in most countries.

### Gender Inequality

In the case of female sex workers, the clients are almost always male. The unequal power relations between the sexes prevent them from effectively negotiating condom use and safer sex, thereby increasing the risk of transmission of STIs. Sex trade is primarily

controlled by a number of stake holders who are in general male. Sex trade is regulated by the law which is often biased against women thereby pushing sex workers to live at the margins of the society. This unequal gender and social status affects their self esteem and confidence to access and utilize relevant STI related services including social entitlements.

## DESIGNING AN STI MANAGEMENT PROGRAM

Four elements that need to be considered in designing an STI control program are:

- Familiarity with the epidemiological patterns and physical and social set-up of the community,
- Development of a service delivery mechanism,
- Development of capacity, and
- Monitoring and supervision.

## Epidemiological Patterns and Set-Up

Data on epidemiological trends and disease profile can be collected from available sources or extrapolated from other similar settings. Information related to the structure and functioning of the sex trade, including specific patterns such as timing, control by different agents and nature of the sex-service delivery settings, e.g., street-based brothel or hotel based, should be collected. Mapping of sex worker would help estimating sex workers population, volume of sex work, types and nature of sex practices, use of condom, etc. The availability and quality of healthcare services, particularly for STIs, and how the community uses them is also essential information. Finally, an understanding of the legal provisions and instruments in the country and how they are implemented in the specific community is useful,<sup>18</sup> for example, in Bangladesh brothel-based sex work is legal; however, it is strictly controlled by the local goons with the collusion of the police. Sex workers have very little autonomy to act in accordance with their own decisions and wishes. Whereas in Thailand, although it is illegal, government and administration are very tolerant of this trade and have adopted a 100% condom use policy through brothel owners with a view to address the HIV epidemic and STI prevention.<sup>20</sup> The 100% Condom Use Program in Thailand has created an opportunity for sex workers to avail and access condom and STI services.<sup>21</sup>

## Service Delivery Mechanism

An effective STI management program addresses prevention and cure simultaneously. The need for partner notification and secondary prevention in sex workers with proven STIs is paramount, while this can be challenging at times. Second, it has to take into account the structure and functioning of the sex trade in that setting. Norms and practices of the sex trade differ—in some places it is a daytime trade, in others it is at night. In some places it is madam-controlled, in others it is controlled by hotel managers, in yet others the women are self-employed. The process

of setting up and managing a service will depend on these and other similar contextual factors. Third, the community of sex workers must be involved from the very beginning in designing and implementing the service. They are an intrinsic part of the solution, as they have the best insight into the situation.

The community involvement has to be incremental over a period of time, based on increasing capacity, confidence and trust. Hence building trust with the sex-workers community is a very important issue at the start of developing a service.

Development of STI service delivery system needs to be considered at two levels: level-1 through outreach component of the program, and level-2 through establishment of a clinical outlet.

## Outreach

An outreach component primarily addresses issues of access and acceptability but will also share responsibility in connection with follow-up of cases, directly observed treatment (DOT), counseling, and partner treatment.

Experience shows that a peer-based outreach program is the most effective model for marginalized and hidden subpopulations.<sup>13,22</sup> Peers can bridge the gap between marginal populations and mainstream services and service providers. They can overcome the cultural barrier in communication. In most circumstances, peers are the best possible agent to reach the hidden population. Through peers, the involvement of the community can be initiated and strengthened, and trust built.

**Peer Led Outreach** Recruiting peers should be based on a clear understanding of their role. Selection of peers should be based on their interest, commitment, verbal communication skills and their acceptability to the community, and not on formal education or age. Self-employed women are likely to be more effective, as in Sonagachi, Kolkata and Tangail, Bangladesh, as they have more autonomy.<sup>6,13</sup> The major task of peers is to deliver a package of preventive and curative services to the end-users. To begin with, they can concentrate on providing preventive messages, the delivery of necessary equipment for prevention (e.g., condoms, spermicides/microbicides) and encouraging the sex workers to effectively negotiate safer sex. They can also assist sex workers to use clinical services and can facilitate overcoming the resistance from the controllers of the sex trade. Gradually, based on the development of requisite skills and experience they will be engaged in improving compliance with treatment regimens, identifying any side effects or problems in taking treatment, and reporting back to the clinic. In spite of limited education, they can effectively maintain records through innovative methods. These records form the basis of the monitoring and information system. Finally, in the third phase, they can be involved in the clinic setting for medical history taking (particularly sexual), drawing of blood samples, physical check-up (weight, blood pressure, and ulcers), and follow-up of patients and administration of DOTs. Following the peer outreach model of Sonagachi intervention program, the Bill and Melinda Gates Foundation developed



an effective intervention in six high prevalence states in India during 2003–2010 covering around three hundred thousands sex workers population through establishing around 370 STI management clinics closest to sex work sites. This is known as AVAHAN program, which adopted community mobilization as the core strategy followed by introduction of peer led outreach and provision of STI services in addition to advocacy component as part of the intervention program. AVAHAN achieved favorable outcome both in stabilizing HIV and STIs among the female sex workers in those intervention areas.<sup>23</sup>

### Setting Up a Clinic

The design of the service delivery mechanism will depend on the type of sex trade—it will vary from brothel-based to street-based. Provision of clinical services through a fixed facility or a mobile clinic or within a drop-in center will be decided based on the setting and availability of resources.

Experience shows that a fixed clinic arranged within or in the vicinity of a red-light district is best suited for a brothel setting as it provides a relatively safe and comfortable social environment for sex workers to come together even for reasons other than STI treatment alone.<sup>14</sup> A clinic within the area of the brothel overcomes barriers related to mobility and restrictions imposed by sex-trade controllers. In case of street-settings, a drop-in center provides a similar opportunity where street-based sex workers can come and relax, and meet other needs including that for STI treatment.

They are more likely to use a center, which meets multiple needs, rather than find the time and opportunity to prioritize only STI treatment. In addition, the drop-in center can also provide the space to organize education sessions reinforcing STI prevention and treatment.

The difficulties faced in setting up a special clinic or drop-in center include limited resources, difficulty in renting an appropriate space and on the part of medical professionals regarding working in such an area and also the practical problems of working at odd hours of the day or night.

A STI clinic is often seen as stigmatized and persons who are availing its services are shy to do so. This applies to sex workers as well; they are not comfortable about going to an STI clinic. Experience from Sonagachi,<sup>13</sup> Kolkata and from other parts of the world confirmed that locating the STI services within a general health clinic is more acceptable. In addition, it meets the other health needs of sex workers and their families. As children and older persons also use the services, it gets less and less associated with sex workers and the stigma is reduced. Over the years, there is a possibility that the clinic will be crowded with patients with general complaints. To overcome this situation and promote greater emphasis on STI, a plan is required. This could be based, for example, on the pricing of services—STI consultation could be free and medication given at a subsidized cost, while general ailments are charged and medication has to be paid for. The timing of the services could be such that the timing allocated for

general services is restricted, while STI treatment is available at all times. People may therefore prefer to seek general treatment from elsewhere.

**Staffing the Clinic** The attitude of the staff towards the sex worker is an extremely important factor to be considered in recruitment. As long as there is a basic acceptance of human beings and openness of mind, the appropriate nonjudgmental attitude of respect can be developed.

Confidentiality requires special attention in this setting. Healthcare providers should not be less serious about maintaining the confidentiality of sex workers. There is a myth that sex workers are “shameless” and therefore do not require discretion and privacy in matters relating to sex and sexual health. Confidentiality must be maintained during history-taking and examination, during disclosure of diagnosis, and maintenance of patient records and files. A system to ensure that confidentiality is maintained at all times has to be installed as otherwise it will depend on individual inclination and cannot be assured.

This system should include specifications regarding physical privacy (a private, secluded space for history taking, examination, privacy during counseling), home and community visits, and maintaining patient records (anonymity of patients in records, and restriction of access to records only to those who must see them for management of the case). As the sex trade is not really legal, police and other law enforcers might wish to track a particular sex worker and ask to see records. The health department may also make demands of this nature, saying it is in the interest of disease control. While establishing the clinic these challenges have to be considered and an arrangement worked out with the necessary public offices to ensure that clinic staff is not pressurized in this regard. Simultaneously, the staff must be well aware of these issues and have the necessary papers, permissions and policy guidelines to support their efforts to maintain confidentiality.

Each clinic should develop a code of medical ethics regarding confidentiality and privacy with respect to STI patients and their partners. This is especially important as partner tracing and treatment is an integral part of effective management. It is necessary to recognize the resistance of partners to visit a clinic meant for sex workers, as the social stigma of being identified as a partner of a sex worker is very high.<sup>8,24</sup> A different service outlet and approach for dealing with the partners of sex workers may therefore be necessary, and every effort should be made to establish linkages for this service.

In addition to the delivery of STI services, the center/clinic should provide a setting for training and upgrading the skills of all staff and of the community.

**Case Management Strategy** In the last decade, several strategies for case management have been tried in different parts of the world. Traditional clinical diagnosis with or without laboratory support and its limitations in different settings forced the scientific community to consider other options such as syndrome based management of major STIs, mass treatment, screening followed by treatment, and a combination of these. There is no single

answer to the question of which is the best approach, as each has its merits and limitations.

The “best approach” also depends on the level of development of STI services in the country, the availability and quality of laboratory services, appropriate human resources, and availability of financial resources. The advantages and disadvantages of each approach in dealing with STIs among female sex workers are discussed below.

The efficacy and efficiency of orthodox clinical diagnosis and treatment has proved to be the lowest. The entire approach depends solely on the individual medical physicians, and their skill to diagnose STI cases based on clinical acumen. The approach is neither standardized nor very sensitive. Wrong diagnosis and inappropriate choice of treatment regimens not only make treatment ineffective but lead to the development of drug-resistant strains of organisms over a period of time. This approach has very little place in the development of STI management programs for sex workers.

**Syndrome-based management:** The advantage of this approach is that a group of symptoms are clubbed together as a syndrome, and treatment is provided to address all the possible infections which cause these symptoms. The choice of treatment regimen does neither depend on individual judgment, nor does it depend on the specialized clinical skill of individuals. The treatment regimen can be standardized according to the prevalence of disease patterns in specific communities and the availability of drugs.<sup>16</sup> The most important advantage is that less qualified personnel can be trained to safely and effectively practice this approach, reaching a higher proportion of patients with better services. This approach provides a greater scope for training even to sex workers/peers in providing the different components of the treatment process, for example, history taking follow-up of cases and ensuring compliance. One of the major limitations of syndrome-based management for sex workers is that the most common clinical symptom in women is vaginal discharge, and it is neither sensitive nor always specific to STIs. A recent review of this approach has indicated that syndromic algorithms have shortcomings, and they should be periodically revised and adapted to the epidemiological patterns of STIs in a given setting.<sup>25,26</sup>

**Etiological approach:** The advantage of the etiological approach is that the patient gets specific treatment for a specific ailment, provided the process of diagnosis and treatment regimen receives quality laboratory support. Therefore, there is less chance of overmedication and indiscriminate use of drugs. The disadvantage is that the patient has to wait for the results of laboratory tests before treatment can be started thereby increasing the risk of transmission of disease during this period. This is an extremely important limitation in a sex work setting where risk of transmission to several people, even within a day seriously compromises the value of this approach for community-based STI programs. While high cost and delay in the availability of results have restricted the use of this option, particularly for sex worker settings, making laboratory services accessible has

presented an additional challenge. However, there has been considerable effort to develop appropriate laboratory based STI diagnosis in the recent past, to deal with symptomatic and asymptomatic presentation of STIs. Non availability of quality laboratory services is a major challenge to implement this approach. However, there is an increasing trend and availability of relatively low cost point of care testing globally. This technological development has cut down the waiting period drastically. As a result of which this approach proved to be beneficial to sex workers in terms of increase in attendance and optimum use of medicine. The global view has been steadily shifting towards laboratory based diagnosis of STI both in the developed as well as in developing countries. There is very little doubt about the emergence of consensus that rapid point of testing of STIs is the way forward in every STI service settings. This approach needs to be made available to sex workers.<sup>15</sup>

One of the major limitations of all the three approaches described earlier is that they only cover symptomatic cases and of these, only those who seek treatment. Major STIs such as syphilis and gonorrhea in females are often (in about 60–80% patients) asymptomatic; this is a problem for partner treatment too. The new developments in STI diagnosis, as indicated above, can be particularly suitable for screening STIs among sex workers.

**Mass treatment:** It implies treating all members of a community, assuming that the infection is widespread. This treatment can be done at regular intervals (biannually or annually). The basic objective is to reduce the pool of STIs in the population at a given point of time, thereby cutting the channel of transmission. The advantage of this approach is that it is simple to administer from the technical point of view. The cost is less over a period of time (compared to clinic-based etiological treatment). Logistically mass treatment can be delivered through a camp-approach, reducing investment in infrastructure and recurring staff costs. This approach also covers many asymptomatic persons who may have infection(s) but will not seek treatment. The limitation of this approach is that where the sexual partner exchange rate is high and the partner stays outside the geographic catchments area, reinfection is common and mass treatment will thus be futile. This approach limits provider-patient dialogue and opportunities for counseling on the preventive aspects. Opportunities for sex-worker community involvement are minimal, and the approach may be viewed as an external initiative, impinging on their rights and choices. Over-treatment is also a limitation. The use of mass treatment in isolation in a sex-work setting therefore cannot be recommended.

However, it can be tried in combination with another approach, e.g., mass treatment followed by syndrome based management of cases or making arrangement of point of care testing in clinic set up dedicated to sex worker population.

**Screening and treatment:** Mass screening of the community members followed by selective treatment is a possible option. At what interval and how this is to be done remains an issue. The advantage of this approach is that it is specific, it can reach

asymptomatic cases, and it reduces the indiscriminate use of drugs. The biggest obstacle is the availability of quality laboratory services for large-scale screening of all major STIs, the prohibitive cost, and the logistics of applying the screening and subsequent follow-up treatment. The option is further compromised in case of sex workers because of the high frequency of partner change and possible exposure to infection on a daily basis. However, the introduction of opportunistic screening among clinic-attendees could improve both the quality of clinic-based service as well as the delivery mechanism by incorporating a percentage of asymptomatic cases.<sup>27,28</sup> Based on the previous discussion about STI management in sex worker populations and the experience gathered in different settings, the authors would like to recommend a fixed general clinic setting with specific emphasis on STI management. The clinic should provide a clear demonstration of condom use in addition to providing condoms. Counseling services should also be made available to clinic attendees to clarify doubts and reinforce messages regarding safer sex. The culture of the clinic should be warm and welcoming, not judgmental, threatening, and alienating. A syndrome-based approach with the gradual introduction of opportunistic screening for one of the major STIs, for example syphilis, and the provision of simple on-site laboratory testing facilities would be the most effective and sustainable. Depending on the development of the program and its impact on the community, gradually more effective strategies vis-à-vis technologies could be introduced to upgrade the program delivery mechanism, such as the introduction of noninvasive laboratory techniques (e.g., a urine test for chlamydia) for all clinic attendees, thereby effectively widening the treatment net. Any approach should view the context as dynamic and be flexible and foresighted enough to take account of this continuous change.

**Linkage with Service Providers in the Locality** No service operates in a vacuum. There are existing local service providers who feel threatened and will therefore, resist the introduction of a new facility. From the beginning, the program should engage with local private service providers in order to soften their resistance, and help them feel comfortable and involved with the service. An effort must be made to obtain their cooperation and assistance in getting referrals and improving the overall quality of services available in the community. For example, inviting them to visit the clinic, arranging training and workshop programs for traditional and other healers, sharing technical and programmatic materials, can improve the relationship with local private providers. Simultaneously, it is necessary to establish a linkage for referring difficult and resistant cases with STIs as well as for other diseases, which cannot be handled at the community clinic. Linkages with reputed laboratories are also required for assuring quality.

## Development of Capacity

Capacity development is an integral part of quality service delivery. First, STI management is still a developing science in many developing countries. STIs should be managed not only at an individual case level, but also at the community level.

Managing STDs at the community level is a challenge because it requires the appropriate mix of skills (as described above) and availability of technology. Second, as existing research proposes an incremental involvement and ownership of the community, it is extremely important to draw guidelines, develop policy and strategy for capacity development of different categories of staff including community members. These should take into account the dynamic context and changing diagnostic tools as well as advances in biomedical intervention. At all points capacity-building is to be viewed as a two-way process where the management including professionals and the community learn from each other in a “learning” atmosphere; it is not the mere transfer of knowledge from top to down in a hierarchical manner.

## Technical Capacity Building

As prevention and care goes hand in hand, all members of the team should have good communication skills in dealing with clients. Staff, including peers from the sex worker community should be acquainted with the newer developments and their implications in their on going program.

The implementers should try to open a dialogue regarding the relevance and appropriateness of the technology for the on-going activities. Besides, the team should be encouraged to acquire skills in critically examining and analyzing the context, e.g., the role of madams and pimps in determining access to service or that of local healthcare providers.

## Monitoring and Supervision

Supervision should be a joint process involving the sex worker community as well as professional staff and management. Usually, supervision and monitoring is seen as a top-down, technical issue that can only be undertaken by highly qualified professionals. On the other hand, experience from different programs has demonstrated the efficacy of community participation. As an STI and sexual practice is such a private issue, whatever the professional skills and tools, they are barely adequate to secure quality information. Representatives of the sex workers, on the other hand, due to their close relationship of trust and deep understanding of the nuances of the business are able to get more accurate and complex information. Importantly, systematic collection of basic data is crucial to inform the program. This included annual mapping of sex establishments and enumeration of sex workers, behavior monitoring (focusing on condom use and number of clients), and STI screening. Monitoring activities would be largely built into the day-to-day activities of the STI clinics, and few special surveys may be required to comprehend service utilization pattern, client’s satisfaction, etc.

Appropriate user-friendly tools can be developed that allow recording and sharing of critical information with the sex trade community, e.g., diagrams indicating access to treatment and condom use through outreach, which are then displayed at the clinic or shared in other ways. This creates a mechanism for regular feedback.



Indicators for the outreach component as well as the clinic component should be correlated and examined for a match at regular intervals. This matching exercise will strengthen the robustness and validity of the information, as well as identify areas that require further attention and indicate where there is inaccurate or incomplete reporting and recording.

## CLINICAL GOVERNANCE, CLINICAL AUDIT, CLINICAL UPDATES

Clinical governance is a system through which clinical service organizations are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish. World Health Organization describes clinical governance as professional performance (technical quality), resource use (efficiency), risk management (the risk of injury or illness associated with the service provided), and patients' satisfaction with the service provided.

The technical quality of STI services for sex workers can be assessed by clinical audit. An in-built system of clinical audit must be a part of the STI management program. A robust evidence-based auditable clinical outcomes should be established. Regular clinical audit cycles should be conducted to assess adherence to the clinical guidelines on a routine basis. The audit should look into regular and complete recording of patient's sexual and reproductive history and diagnosis, the adherence to treatment guidelines (e.g., closely following the standard flowchart for treatment, adopted by the program). The audit will also enquire into client satisfaction, effective communication between doctor and patient (e.g., whether patients understand the treatment regimen and could express difficulties in following treatment directives). This process examines the performance of all categories of staff in an open and transparent manner, allowing each one to reflect on their work and to identify steps to rectify shortfalls themselves, without blame. It further reiterates the value of the contribution of each and every staff. This process empowers different categories of staff and essentially breaks the hierarchical structure in favor of a more horizontal one.

Clinical update will involve reevaluating-service training, multi-disciplinary team meeting to discuss difficult clinical cases, journal clubs, attending conferences and other learning opportunities. There should also be learning facilitation utilizing external agencies, at least annually. Exchange visits with other relevant institutions are also highly recommended.

## Conclusion

The approach towards STI management presented in this chapter looks at the issue in a wider perspective—that of management of STIs at a sex-worker community level, rather than only at an individual patient or case level. The intention is not to undermine the role of medical professionals, as the value of their expertise is clearly irreplaceable. Their role would be viewed as leaders of a multidisciplinary team where the active

involvement of the community is essential. In the past purely biomedical approach has been limited in dealing with the various barriers to effective treatment seeking behavior and practices, including primary prevention. The authors have tried to highlight the importance of long-term sustainability through fostering community involvement and ownership. Medical professionals have a responsibility as well as an important role in building appropriate capacity in the community and in re-examining their own values and practices through a process of sharing and learning. As team-leader, medical professionals have to use their expertise in finding the best specific solution and designing the best suited services for each context—there is no single “model” that is ideal in all settings.

Community management of STIs in sex workers cannot follow a prescriptive model. The situation is in a state of constant development and flux and so is the level of knowledge and technology. An effective strategy is one where this changing scenario is recognized and re-examined regularly and the program is accordingly restructured and revised. One needs to be open to newer strategies and tools of interventions, e.g., voucher scheme, opportunistic screening, point of care testing etc., and would decide to include or exclude those based on the perspective of sex work settings and availability of tools and finances.<sup>28–30</sup> In this respect, the clear direction of travel towards low cost point of care testing is increasingly adopted globally. This could improve the quality of care for STIs in female sex workers, who are increasingly valuing this approach.

The dynamism within the community of sex workers also influences the outcome of the program. The responsibility of the team-leader includes being fully aware of these forces and the ability to make necessary adjustments in the program. Keeping in view the aspirations and skill development in the community, there will be a need to modify and upgrade the program periodically.

One of the major challenges the team-leader faces is the low priority and stigma that STI management receives within and across the medical world. Some efforts have to be made to influence policy-makers and leaders, including the medical community to change attitudes towards sex and sexuality and STIs.

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# Sexually Transmitted Infections Associated with Sexual Assault

P. Janet Say

96

## Introduction

Sexual assault is defined as an act of a sexual nature on another person without their consent. It can range from fondling to forcible penetration, and may often, particularly in the sexual assaulted adult males, be associated with other physical violence. It may involve the use, or threat of force or maybe performed on a victim unable to give consent because of their age and/or physical or mental disability.<sup>1</sup> Different countries have different legal categories of sexual assault. The different definitions can range from terms such as unlawful sexual connection to “eve teasing” and there are often differences between male and female sexual assault legal nomenclature. These categories are necessary to define the gravity of the offence and guide subsequent sentencing.

Sexually transmitted infections (STIs) are often an unwanted consequence following sexual assault. The possibility of HIV transmission during the sexual assault has further added to the panic and stress related to sexual victimization.<sup>2</sup>

Both male and female, adult and child, victims of sexual abuse are at risk of acquiring a sexually transmitted infection. Doctors examining and treating such patients require knowledge of STIs on which to base their clinical care and forensic opinion. The brief notes provided in this chapter are not, however, a substitute for keeping up-to-date with the current literature in this rapidly expanding field. Optimal management of STIs, particularly in children, may also require consultation with a specialist in sexual health as well as pediatricians.

## Epidemiology of Sexual Assault

Only a minority of sexually abused children in developing countries receive a medical examination, which includes optimal STI screening. The same is true for adult victims of abuse—only a very small percentage of whom ever present to an official agency.<sup>3</sup> In the USA for every sexual assault reported, 3–10 are unreported, one in 3 women worldwide has experienced sexual assault or rape.<sup>4</sup> The criminal offence of rape in marriage is being increasingly recognized in developing countries, e.g., India.

One in 6 or 7 rape victims in the USA are male.<sup>5</sup> An analysis of 120 studies of prevalence of sexual assault in the USA showed 13% of women and over 3% of men reported being raped. Attempted rape was reported in 18% of women and 6% of men, and sexual assault was reported by 22% of women and 14% of men.<sup>6</sup>

## Epidemiology of STI in Sexually Assaulted Adults

In an adult who has a history of consenting sexual activity it may be difficult to attribute the acquisition of the STI from an alleged offender. Gonorrhea, Chlamydia, and *Trichomonas* in women are often asymptomatic and can be pre-existing before the event.

Davis<sup>7</sup> showed that of 110 women seen at the Sexually Transmitted Infection Clinic in Birmingham, UK, who claimed to have been raped, 14% had STIs, of which 8% had chlamydia and 6% *Trichomonas*. Wintle's audit in Auckland showed 11.9% had an STI with 6/109 women undergoing a forensic examination having chlamydia, gonorrhea or both infections.<sup>8</sup>

The risk of acquiring an STI consequent to sexual abuse varies with the disease prevalence among offenders and the nature of the sexual contact. The factors which influence disease prevalence among offenders include its prevalence in the general population, the local incidence of disease, and the incidence of particular infections in high-risk activity groups (e.g., hepatitis B virus, HIV). The factors related to the sexual act which affect the risk of acquiring an STI include the nature of the sexual act (e.g., vaginal or anal penetration), the degree of trauma present, and whether body fluids were exchanged.

The most likely infections for which these patients are at risk appear to be genital warts, chlamydia, gonorrhea, genital herpes, trichomoniasis, syphilis, and HIV.<sup>9</sup> All these infections (except HPV) are now documented in various studies to be associated with a higher risk for acquisition of HIV.

## Sexual Assault in Adult Males

Anal penetration occurs more commonly in male rape with skin and mucosal damage occurring in up to two-third of victims,<sup>10,11,12</sup>



and thus males are at a higher risk of acquiring infections such as hepatitis B virus and HIV. De Visser reports on experiences of sexual coercion among a representative sample of adults. A telephone interview was completed on 10,173 men and 9134 women aged 16–59 years with a response rate of 73.1%. In the study 4.8% of men and 21.1% of women had experienced sexual coercion and 2.8% of men and 10.3% of women had been coerced when aged 16 or younger. Adverse outcomes in males included increased risk of history of STIs, increased smoking, and drug use as well as avoidance of sex. 2.6% of males compared to 7.3% of females reported to the police.<sup>13</sup>

Men who have sex with men (MSM) were 5 times more likely than heterosexual males to have suffered sexual assault and this is possibly related to their higher number of partners, the situations in which they seek sex, and the phenomenon of gay bashing. Overall most males were less likely to present to health agencies for disclosure because sexual assault is generally thought to be a female issue; it infers a loss of masculinity or male weakness and the possibility of being labeled homosexual.<sup>14</sup> Sexual identity and orientation can be confused and sexual dysfunction may follow. It is common for arousal, even ejaculation, to occur in males who are groomed during the assault.<sup>15</sup>

A single episode of receptive anal intercourse with an HIV-positive male in Australasia has a risk of approximately 1 in 100–200 of transmission of HIV compared to insertive anal and vaginal intercourse of 1:1000, but HIV post exposure prophylaxis (PEP) should be offered in these situations.<sup>16,17</sup>

Reeves et al. report on a review of the forensic notes on 92 males in London of those 30% were heterosexual and 34% were homosexual; there was no information regarding the rest. The majority (79) were referred to the police. Non genital injuries were documented in 40% and anal injuries in 34%. HIV PEP was commenced in 23 of the 54 men reporting rape and 14 of the 31 with anal injuries.<sup>18</sup>

A telephone interview study of 8005 males and 8000 females in USA confirmed that 219 males had been sexually assaulted, a prevalence of 3%. 11% had undergone physical violence, 31% had been raped anally, and in 5% weapons were part of the attack, 29% sought help but only 19% reported to the police.<sup>19</sup>

## Epidemiology of Sexual Assault in Resource Poor Nations

The World Health Organization (WHO)<sup>20</sup> has recognized the importance of sexual assault in the spread of HIV particularly in Third World countries where the disease may be endemic and multiple economical, sociocultural factors add to the risk of its spread.<sup>21</sup> In undeveloped nations intimate partner violence (IPV)<sup>22–24</sup> may not be acknowledged let alone legislated for. Many countries are war zones and rape may be part of torture of females<sup>25</sup> as well as males.<sup>26</sup> Coercion is as common as much as in developed nations, but the imbalance of power in many countries between males and females is a very important factor.<sup>27</sup> Poverty is a driving force for “survival

sex” in street kids, the trafficking of children into sexual slavery and also it encourages the “sugar daddy” phenomenon, as in Africa. In a study of HIV prevalence in sex trafficked Nepalese girls 38% tested positive for HIV and the median age of trafficking was 17 years with 14.7% trafficked before the age of 15 years. Those under 15 years were at increased risk of HIV, particularly if they were trafficked to Mumbai.<sup>28</sup>

Childhood sexual abuse (CSA) has been quoted as less than 4% overall in China, but in Chen’s paper 1 in 5 young women (21.9%) reported at least one type of child sexual abuse before the age of 16 years.<sup>29</sup>

Lalor’s literature review of child sexual abuse (CSA) in sub-Saharan Africa estimated that approximately 0.6–1.8% of all children in high HIV incidence countries in South Africa would experience penetrative sexual abuse by an AIDS/HIV infected perpetrator before 18 years of age. This would be in comparison to Ireland where the risk is 0.004%.<sup>30</sup> The same author described how CSA had increased in Tanzania possibly because of the idea that one “may cleanse” oneself of AIDS and other STDs by having intercourse with a virgin or young girl. Sixty five per cent of Tanzanian members of parliament felt that witch doctors were making defilement of children or incest a condition for their customers in obtaining wealth or solving their problems.<sup>31</sup>

Worku et al. studied childhood sexual abuse and its outcomes in female high school students in Ethiopia and of 323 students, 68.7% reported CSA, 7.2% of these had an unwanted pregnancy, and 5.9% had sexually transmitted diseases.<sup>32</sup>

The WHO is concerned at the effect of IPV and sexual violence on the HIV epidemic. An expert meeting occurred in May 2007 to discuss measures of prevention and tabulated the factors associated with IPV for the victim and the perpetrator as well as those associated with sexual violence.<sup>33</sup>

More than 1 in 3 married Bangladeshi men reported physically and/or sexually abusing their wives in the past year. They were also more likely to report both premarital and extramarital sex partners. On top of that they were less likely to disclose STI symptoms or infection to their wives, i.e., discharge from the penis, a sore or ulcer on the penis, or dysuria in the past year.<sup>34</sup>

A study from Goa in India concluded that socioeconomic deprivation and gender disadvantage were associated with a raised risk of reproductive tract infections, e.g., bacterial vaginosis (BV). The risk factors for STIs included the indication that disadvantaged women were likely to be infected by their husbands.<sup>35</sup>

Similarly, a further longitudinal study in women in Goa showed that spousal sexual violence and poverty were risk factors for incident STIs in women. Of 2180 women followed up 101 (4%) had an STI at baseline. At 6 months 37 (1.8%) had an STI, chlamydia (13), gonorrhea (14), trichomonas (9) and one had both gonorrhea and chlamydia.

At the 12-month visit 991 women were screened and 28, i.e., 1.4% had an incident STI, chlamydia (9), gonorrhea (8),

trichomonas (10) and one with dual gonorrhea and chlamydia. The findings support the previous cross sectional study that women were likely to be infected by their husbands.<sup>23</sup> In other studies this has included acquisition of HIV infection by married, monogamous women in India.<sup>36</sup>

Acute trauma following sexual assault can lead to complications such as labial adhesions.<sup>37</sup> A study of 4715 women and girls who had suffered sexual violence in the Congo between 2003 and 2006 showed 702 had been left with genital fistulae.<sup>38</sup>

## Alleged Offenders

The incidence of STIs in alleged offenders is unknown as it is unusual for them to be examined. Giedinghagen<sup>39</sup> described a group of 75 children where their alleged offenders were examined for gonorrhea, 17% of offenders were culture positive. Physicians examining complainants of sexual abuse should encourage the screening of alleged offenders for the presence of STIs. However, consent involving very careful pretest counseling, that is well-documented, should be adhered to because of the legal implications of using evidence against possible offenders. STIs may be more common in some sexual offenders compared to the general population, and screening should be undertaken whenever possible. Detection of an STI will alert the physician to the likelihood of infection in a victim so that appropriate investigation, treatment, and long-term follow-up can be instituted (see Table 96.1). It may also have valuable forensic implications, which may provide corroborative evidence of a sexual assault for care and protection of the child or prosecution of the offender in court.

It will also alert the physician to the need for contact tracing other sexual contacts of the offender (e.g., adult sexual partners, other children in the family) and may result in a guilty plea by an offender thus avoiding the need for a court appearance by the victim. Further it may become an issue in victim compensation if contraction of a specific sexually transmitted disease can be proved to result from an assault. This has become more important with refined methods of DNA finger printing available for epidemiological typing. A negative screening of the alleged offender allows the physician to reassure the victim that the likelihood of having contracted a sexually transmitted disease from the assailant is minimal and may obviate the need for some screening procedures in the victim. It should be remembered, however, that the sensitivity of most diagnostic tests is not 100%. A clinical decision should be made whether to screen a victim despite negative testing of the offender.

## Relevance of Sexually Transmitted Infections in Medical Management of Sexual Abuse

The health of the sexually assaulted individual can be jeopardized if there is no adequate post-assault medical management. The increasing prevalence of viral STIs with long-term complications

**Table 96.1:** Suggested Optimum Screening for Sexually Transmitted Infections in Alleged Male Sexual Offenders\*

<b>Inspection</b>		<ul style="list-style-type: none"> <li>• Urethral discharge</li> <li>• Ulcerated lesions</li> <li>• Warts</li> <li>• Molluscum contagiosum</li> <li>• Pediculosis pubis</li> <li>• Enlarged inguinal glands</li> </ul>
<b>Swabs</b>	Urethra	<ul style="list-style-type: none"> <li>• Direct Gram stain</li> <li>• Culture for gonococci</li> <li>• <i>Trichomonas vaginalis</i> culture (if available)</li> <li>• Herpes simplex if indicated in viral transport medium or PCR</li> </ul>
	Urine	<ul style="list-style-type: none"> <li>• <i>Chlamydia/Gonorrhea</i> NAATs × 2</li> <li>• TYM culture for <i>Trichomonas</i> if indicated</li> </ul>
	Rectum** & throat	<ul style="list-style-type: none"> <li>• Culture for gonococci</li> <li>• Culture for <i>Chlamydia</i> (if available) (NAATs × 2?)</li> </ul>
	Ulcerated lesion	<ul style="list-style-type: none"> <li>• HSV culture (viral transport media) or PCR? <i>T. pallidum</i> consider dark ground microscopy/Direct FTA</li> </ul>
<b>Blood</b>		Serology for: <ul style="list-style-type: none"> <li>• Syphilis (VDRL, RPR, TPHA, EIA)</li> <li>• HBV**</li> <li>• HIV***</li> <li>• HCV (? drug user)***</li> <li>• HSV 1 &amp; 2</li> </ul>

\*Female offenders should be screened as for adult female victims.

\*\* If past activity such as receptive anal intercourse is suspected.

\*\*\*A careful sexual history and discussion of the implications of the test result are preliminaries to taking this test.

Abbreviations: NYC, New York city medium; TM, Thayer–Martin medium; NAAT, nucleic acid amplification test; EIA, enzyme immunoassay.

are of particular concern because there is, as yet, no curative treatment, and long-term management by physicians with specialized knowledge is required.

Knowledge of STIs is essential for planning assessment and management of patients who have been sexually abused, and includes causative organisms and their incubation periods, clinical syndromes, diagnostic procedures, disease prevalence, relative risk of specific disease acquisition, and interpretation of results including their forensic relevance.

Advice on the risk of acquiring an STI, optimal screening for the presence of an STI (see Table 96.2), optimal timing of such screening (particularly in children when this should be kept to a minimum), advice on prophylaxis for STI, treatment of any diagnosed STI, short-term follow-up including sexual contacts of the patient, long-term follow-up (particularly for viral STIs—onward referrals, where indicated), and screening of alleged perpetrators and their contacts if indicated.

Apart from clinical care, investigation, and treatment, evaluation of victims has forensic implications. Briefly, the presence of certain STIs is one of the most objective indicators of sexual abuse in children and may occasionally be relevant in adult rape. Further, forensic opinion is dependent upon careful adherence to detail

**Table 96.2:** Recommended Optimum Screening for Sexually Transmitted Infections in Adult or Adolescent Women

<b>Urethral</b>	<ul style="list-style-type: none"> <li>• Direct Gram stain</li> <li>• Swab in Amie's transport medium (Gonorrhea) or NAATs × 2</li> <li>• Direct plating on to NYC or TM media</li> <li>• <i>Chlamydia</i> NAATs × 2</li> </ul>
<b>Vaginal</b>	<ul style="list-style-type: none"> <li>• pH</li> <li>• Direct Gram stain</li> <li>• Wet Preparation (if possible) × 2, i.e., saline and 10% KOH</li> <li>• HVS in Amie's medium</li> <li>• Direct plating SABDEX for yeasts</li> <li>• Swab in TYM broth for <i>Trichomonas</i> culture (if available)</li> <li>• Whiff test with 10% KOH</li> </ul>
<b>Cervical</b>	<ul style="list-style-type: none"> <li>• Direct Gram stain</li> <li>• Swab in Amie's medium (Gonorrhea) or NAATs × 2</li> <li>• Direct plating NYC or TM</li> <li>• <i>Chlamydia</i> NAATs × 2</li> </ul>
<b>Rectal</b>	<ul style="list-style-type: none"> <li>• Swab in Amie's medium (Gonorrhea)</li> <li>• Direct plating TM</li> <li>• <i>Chlamydia</i> (culture necessary, if available) (NAATs × 2)</li> </ul>
<b>Throat</b>	<ul style="list-style-type: none"> <li>• Swab in Amie's medium (Gonorrhea)</li> <li>• Direct plating on TM media</li> <li>• <i>Chlamydia</i> (culture necessary, if available) (NAATs × 2)</li> </ul>
<b>Urine</b>	<ul style="list-style-type: none"> <li>• NAATs × 2 <i>Chlamydia</i> (and Gonorrhea screening) if available</li> </ul>
<b>Blood</b>	<ul style="list-style-type: none"> <li>• EIA, RPR (VDRL), TPHA repeat after 3 months</li> <li>• ? HIV, HBV, HCV (if indicated)</li> </ul>
<b>Ulcerated lesions</b>	<ul style="list-style-type: none"> <li>• Swab in viral transport medium for herpes or PCR</li> </ul>

Abbreviations: NYC, New York city medium; TM, Thayer–Martin medium, 10% KOH (potassium hydroxide); EIA, enzyme immune assay; RPR, rapid plasma reagin; TPHA, *Treponema pallidum* hemagglutination test; NAAT, nucleic acid amplification test.

regarding the chain of evidence and procedures for collection of laboratory specimens. Opinion on the significance of a particular STI in relation to likelihood of sexual abuse may be needed for child protection and judicial agencies (see Chapter 108).

## Sexually Transmitted Infections in Sexually Abused Adults and their Forensic Relevance

### GONORRHEA

The disease affects columnar epithelium of the urethra, throat, rectum, and cervix of adults. The incubation period is 3–5 days in adult males (with urethritis) and up to 14 days or longer in females. Throat, cervical, and rectal infections are often asymptomatic. Acute cystitis may present or pelvic inflammatory disease may develop and lower abdominal pain may be the cause for admittance of a young/adolescent female to a pediatric ward. In low incidence populations infection may have forensic relevance occasionally in adults, particularly in virgins.

### CHLAMYDIA TRACHOMATIS

Infection of *Chlamydia trachomatis* is usually asymptomatic in adult women and post pubertal female adolescents (up to 85%) and 25% in adult/adolescent males.<sup>40</sup>

Anecdotally, *C. trachomatis* has been shown to be present in the cervical mucosa of an adult 6 years after possible acquisition of the organism. It is probably the commonest STI liable to be contracted post sexual assault and prophylaxis should always cover for this infection.

Lymphogranuloma venereum (*C. trachomatis* L<sub>1</sub>, L<sub>2</sub>, L<sub>3</sub>) is now described in many countries in MSM populations, usually as a rectal infection that requires 3 weeks of doxycycline treatment. It has not yet been identified as acquired post sexual assault.

### TRICHOMONAL INFECTION

*Trichomonas vaginalis* is an STI with an incubation period of 7–28 days. It may present late, after gonorrhea or chlamydia diagnosis in women as a green, frothy, fishy smelling discharge. The prevalence of disease increases with age in women. *Trichomonas* in adult women can occasionally be transmitted during sexual assault and rarely has been shown to have forensic relevance.

### SYPHILIS

Syphilis serology should always be done as part of an STI screen associated with sexual assault. Post assault antibiotic prophylaxis against STIs should optimally include an agent which is treponemacidal. In low-risk adult populations syphilis acquisition may be a marker for sexual assault. The person should have follow-up serological screening at 3 months after the last abusive incident.

### HUMAN PAPILLOMAVIRUS (HPV) INFECTIONS (GENITAL WARTS)

Over 150 types of human papillomavirus are known; about 24 types are known to infect genital squamous epithelial cells which undergo transformation and proliferation. The incubation period varies from 4 weeks to 2 years. Cases of genital warts may follow sexual assault in both male and female adults but relating their acquisition to the assault is problematic in most cases.

### VULVOVAGINAL CANDIDIASIS

Asymptomatic vaginal carriage is common in young women and trauma may encourage infection presenting post assault. Candidiasis can produce nonspecific changes, i.e., redness, superficial ulceration, and fissuring that should not be confused with traumatic effects at the acute examination.

### BACTERIAL VAGINOSIS

BV is an overgrowth of many bacteria, particularly anaerobes and mycoplasmas, at the expense of resident lactobacilli.



BV is not yet thought to be a sexually transmitted infection but is associated with sexual activity, consenting or nonconsenting. Prophylactic antibiotic regimens are often used for this common condition post assault.

### GENITAL HERPES INFECTION

The majority of genital infections in adults are caused by HSV-2 virus, although, increasingly common type 1 infection is isolated in the genital region. The incubation period varies from 2 to 20 days (usually 2–5 days). In a previously sexually active adult, forensic relevance is questionable, unless symptoms occur post assault, with seroconversion confirmed by herpes serology.

### HUMAN IMMUNODEFICIENCY VIRUSES (HIV-1, HIV-2)

The incubation period for seroconversion varies from more than 2 weeks up to 2–3 months in the vast majority of cases.

Acquisition of this infection is the most feared sequelae following sexual assault. PEP following sexual assault is available.<sup>16</sup> HIV infection following rape has been reported.<sup>41–43</sup> Hillman<sup>10</sup> pinpointed the need for an increased awareness among the general public of male sexual assault and the increased risk of acquiring HIV infection in this group.

### HIV Prophylaxis after Sexual Assault (PEP) (Table 96.3)

Post exposure prophylaxis should be given optimally within 1 hour and up to 72 hours where there is a high-level exposure to HIV. The risk for acquisition post-rape may depend on the type and length of time of sexual contact, the extent of trauma or presence of STI or genital ulcerative disease in the victim, and the likely incidence of HIV disease and viremic state of the alleged assailant.

In high-risk situations, it is appropriate to administer combination therapy for 4 weeks. Triple therapy is indicated in very high-risk situations.<sup>16</sup> The patient must be fully counseled on the risks of side effects and long-term complications, as well as carefully followed up. Follow-up includes monitoring of side effects, blood tests, and HIV screening at 4 weeks, 3 and 6 months.

Burgess<sup>44</sup> discussed the ethical dilemmas of HIV and rape, concentrating on the need for legislation to protect both the victim and assailant from misuse of data of seropositivity. The ethical considerations in testing victims of sexual abuse for HIV infection were reviewed by Fost.<sup>45</sup>

**Table 96.3:** Indications for HIV Testing and Possible PEP

Victims	Assailants
<ul style="list-style-type: none"> <li>Clinical profile consistent with AIDS</li> <li>Parent/victim insisting on test</li> <li>Anal rape, trauma genitally</li> </ul>	<ul style="list-style-type: none"> <li>High-risk behavioral profile</li> <li>HIV seropositive known or suspected</li> <li>Multiple assailants</li> </ul>

### GENITAL MYCOPLASMA INFECTIONS

The common agents are *Ureaplasma urealyticum*, *Mycoplasma hominis*, and *Mycoplasma genitalium*. Incubation periods are not completely elucidated yet, however, for *U. urealyticum*, it is about 14 days.

*U. urealyticum* and *M. hominis* are commonly isolated from the vagina of asymptomatic sexually active adult females. Colonization in adults by *U. urealyticum* has been shown to correlate with sexual activity.

*M. genitalium* has not yet been reported post sexual assault but has probably occurred as it is found in 10–20% of NSU in developed nations and has higher rates in some surveys in African countries.<sup>46</sup> Theoretically, antibiotic prophylaxis regimens commonly used post assault include cover for BV, chlamydia, gonorrhea, and *M. genitalium* (Azithromycin).

### HEPATITIS B VIRUS INFECTION

The incubation period for this double-stranded DNA virus varies from 40 to 110 days approximately.

Sexual transmission is a major route for transmission of hepatitis B in adults in western society.<sup>47,48</sup> Sexual assault, particularly anal penetrative sex, also with genital injury and/or bleeding increases the likelihood of transmission where the alleged offender is a carrier of hepatitis B virus, especially if 'e' antigen is positive. Hepatitis B vaccination should be considered in cases of adult sexual assault particularly in countries where increased incidence is likely, or in high-risk populations.

### HEPATITIS C VIRUS INFECTION

The incubation period for this enveloped RNA virus is similar to hepatitis B, 40–110 days approximately. Various studies indicate the rate of sexual transmission at about 5–10%,<sup>49</sup> but this has not been confirmed in some studies more recently.

It is not yet possible to evaluate the importance of hepatitis C in sexual assault. Screening for hepatitis C antibody and antigen may be performed if the alleged assailant is in a high-risk group for carriage of the virus, i.e., intravenous drug user. There is no vaccine available as yet and no method of prophylaxis.

## Sexually Transmitted Infections in Adult and Adolescent Victims of Sexual Assault

It is important to discuss the possibility of contracting STIs and prophylactic treatment recommendations with the patient and obtain consent for baseline and NAAT tests for chlamydia and/or gonorrhea, serology for hepatitis B, syphilis, and HIV.

The patient may already have STIs prior to the assault. Treatment based on specific diagnosis is more effective. Single-dose treatments at the time of initial examination are advantageous for sexual assault victims as compliance and follow-up with a multiple-dose regimen is often low.

For gonorrhea, a single-dose regimen effective against both gonorrhea and incubating syphilis should be preferred.<sup>50,51</sup>

Regimens including ciprofloxacin may be contraindicated in pregnancy and quinolone-resistant strains are common in Asia. Spectinomycin is safe in pregnancy but unreliable for throat carriage and not always available. All the regimens for gonorrhea should be followed by concomitant treatment for *Chlamydia* (*M. genitalium* cover as well preferably) and BV. Prophylactic antifungal anticandida treatment can also be offered.

## PROPHYLAXIS FOR STIs

In most cases of suspected child sexual abuse, prophylaxis is not indicated.<sup>51</sup> Prophylactic therapy is recommended when the child has had contact with an individual known to have a sexually transmitted infection, or has been sexually assaulted by a stranger and when the physician suspects the child will not return for follow-up, or if there are signs and symptoms but inadequate screening. Where there is a strong indication of abuse, but inadequate screening is carried out, consider prophylaxis.

Immediately after adult rape, prophylaxis should be aimed at ascending bacterial infection such as gonorrhea and chlamydia which can cause pelvic inflammatory disease within 48 hours. Rambow et al.<sup>52</sup> reiterate the need for prophylaxis as their study showed a follow-up rate of only 30%. However, for some, prophylactic treatment may act as a disincentive to return for the follow-up when tests will be more accurate. The CDC guidelines include cover for trichomonas and bacterial vaginosis.<sup>50</sup>

Patients often benefit psychologically from taking prophylaxis as this gives them a feeling of taking control over the risk of infection. Prophylaxis is not guaranteed for any of the viral STIs and especially in those with longer incubation periods. It may be offered, in very special circumstances, for HIV. Prophylaxis against HIV (PEP) requires specialist consultation.<sup>16</sup> Hepatitis B vaccination should be made available where indicated and can be started up to 14 days following sexual assault, the first of a three-dose hepatitis B vaccine course is given, hyperimmune gamma globulin is very rarely indicated. Education about long-term follow-up is mandatory.<sup>53</sup>

## FOLLOW-UP CARE

The importance of follow-up and a clearance STI screen cannot be over emphasized. The onus to arrange follow-up rests with the treating doctor, be it a general physician, sexual health physician, or pediatrician. Failure to do this may have serious consequences such as failure to ensure immunity to hepatitis B and pelvic infection to prevent future infertility, syphilis—secondary and tertiary disease, cervical dysplasia/neoplasia associated with HPV infection, HIV/AIDS, and reinfection from continual abuse.

Follow-up assessments also present the doctor with an opportunity to ensure that a child or young person is free of further abuse and that rehabilitative therapy is taking place. The timing of the follow-up should be rationalized and kept to a minimum by consideration of incubation periods, results from screening the offender, and potential consequences.

Although follow-up screening is essential for proper care, it is often missed because the victim fails to return.<sup>8</sup>

At the initial examination, the adult or adolescent patient needs to be instructed on possible symptoms of a sexually transmitted disease and urged to attend the STI Clinic for follow-up examination when diagnostic tests can be performed. The timing of follow-up screening will also depend on whether baseline screening was carried out and/or prophylaxis was given. The following time frames are suggested. At 2–4 weeks, examination and STI screening should be encouraged. At 3 months, syphilis serology, hepatitis B and HIV antibodies need to be done, where applicable.

If counseling is ongoing, the counsellor should reinforce the need for follow-up medical examination. On occasions medical treatment is indicated for post traumatic stress disorder. The presence of the same STI in victim and perpetrator has been useful in the court, i.e., sometimes in causing the perpetrator to change his plea.

Sexual abusers are often multiple offenders. Where a sexual offender is identified as a source of infection and she/he could have had access to other children in the family, all the children, if possible, should be screened. Where there is no disclosure by the child, screening adult members of a household has often identified carriers of infection. Informed consent is required for such screening (initial screening on urine specimens with NAATs may be very useful if large numbers are involved).

In the case of adolescent and adult victims of sexual abuse, contact tracing of the victim's own peer sexual partners as well as the abuser is important both to stop the victim becoming reinfected as well as to protect the partners.

### Summary

Sexual assault in adult and adolescent males and females has serious consequences affecting the physical, sexual, and mental health of the complainant. There is ample evidence for the cost effectiveness of dealing with acute and chronic post-traumatic stress disorder that commonly occurs. There is a high risk of psycho, socio, and sexual dysfunction that otherwise may follow, putting burdens on communities. For the individual assaulted, immediate medical care provided through sexual health clinics by practitioners trained in medico-legal medicine, with follow-up care also offered, is optimal. STI prophylaxis, PEP, and emergency contraception may be necessary in patients whether or not they are making a formal complaint. In resource-poor nations, in war zones, in countries with gender inequality, health budgets directed towards the assaulted may be pitiful at present. However, the WHO has acknowledged that violence including sexual violence needs to be addressed to help stop the spread of AIDS to many victims of assault, particularly wives and children.

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# 97

## Sexual Health of Migrant Populations

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### Introduction

In the 21st century, it is commonplace for individuals to move either temporarily or permanently between countries or within their own country as internal migrants or displaced persons. People may choose a permanent move for a wide variety of reasons such as relocating for a safe sanctuary from areas of conflict or persecution, education, work or in search of a different lifestyle. The number of people residing outside their country of birth is at an all-time high of over 200 million, more than double the number a generation ago.<sup>1</sup> Migrants are an enormously diverse population and fall into a number of different categories with different ethnicities, cultures, beliefs, and religions (Fig. 97.1). The majority of migrants will fall into a group named *economic migrants*. These are individuals and their families (mostly for reunification) leaving their country of birth to improve their quality of life and may include long-term migrants or short-term seasonal workers. *Frontier workers* are migrants who retain their usual country of residence but work in a neighboring state returning daily or weekly. *Refugees* are people with a fear of persecution for reasons of race, religion, nationality, membership of a particular social group or political opinion, who enter a country and claim asylum under the 1951 Geneva Convention. Once the fear has been proven to be well-founded, the claimant is granted refugee status. *Asylum seekers* are people who have fled to another country where they have applied for state protection by claiming refugee status, but have not received a final decision on their application. *Irregular or undocumented migrants* are people without legal status owing to illegal entry or the expiry of their visa. *Displaced persons* are people fleeing an armed conflict or escaping natural or man-made disasters or their effects. This term primarily covers persons displaced within the borders of their country of origin (i.e., internally displaced persons). A particularly vulnerable group of migrants are *trafficked individuals*. The trafficking of individuals is defined by the protocol against trafficking as “the recruitment, transportation, transfer, harboring or receipt of persons, by means of the threat or use of force or other forms of coercion, abduction, fraud, deception, abuse of

power or a position of vulnerability or of the giving or receiving of payments or benefits to achieve the consent of a person, having control over another person, for the purpose of exploitation”.<sup>2</sup> A final significant contributor to the migrant population are the *international students*. They move to benefit from opportunities and academic programs offered by countries and educational institutions.

Many of these groups will have needs similar to their host country peers whereas others will have very different concerns and requirements including issues related to their sexual health.



Fig. 97.1: Bangladeshi migrants in London.

## Socioeconomic Issues

If socioeconomic issues are not addressed in the migrant population, their priority may just be to survive in a hostile environment rather than to look after their sexual health needs. In 2009, there were 36.5 million refugees under the care of The Office of the United Nations High Commissioner for Refugees (UNHCR) while the number of internally displaced persons in armed conflict situations was estimated at 27.1 million.<sup>3</sup> The degree of vulnerability in which migrants find themselves depends on a wide variety of factors, ranging from their legal status and government policies to their overall environment.

### IMMIGRATION CONCERNS

Laws that prevent migrants from accessing healthcare based on their immigration status are on the grounds of cost to taxpayers to fund their healthcare needs and that excluding them from social benefits would serve to deter future irregular/illegal migrants. Government policies may prevent internal migrants from one part of the country in accessing healthcare in another part. However, governments have legal obligations in relation to the health of every person within their jurisdiction under human rights legislation. National healthcare plans often discriminate against temporary migrants especially undocumented ones by making only emergency care available for noncitizens. Consequently, these migrants may initially self-medicate or consult quasi-medical practitioners within their community. Additionally irregular migrants may have concerns that health providers may have links to immigration authorities and that seeking care will highlight their illegal status. Migrant workers who have gone to considerable trouble to find work abroad, when diagnosed with a sexually transmitted infection in the host country may lead to their repatriation. As a consequence many migrant workers may prefer not to attend health services at all, further contributing to their vulnerability.<sup>4</sup> Professional confidentiality should be promoted and protected by the law, and support should be provided to health professionals in upholding this principle in the context of working with undocumented migrants.<sup>5,6</sup>

### INCLUSIVE SERVICES

In some countries, legislation has been implemented in favor of universal access to care and treatment of infectious diseases. For example, in the UK and Germany, infectious diseases are diagnosed and treated free of charge. However, in relation to other health problems such as mental health, where the benefit to the general public is not directly obvious, services are rarely available for irregular migrants.<sup>7</sup>

There are positive initiatives occurring among some large transnational corporations to ensure affordable and accessible healthcare for migrant workers and their families. Some of these companies realized the threat to productivity posed by poor health, especially HIV/AIDS and tuberculosis. In parts of southern Africa, for example, AIDS-related illness and death

has reduced the workforce by 20%.<sup>8</sup> Thus many corporations are collaborating with each other and with governments and civil society to tackle diseases such as HIV/AIDS.<sup>9</sup> The southern African mining industry, which depends almost entirely on migrant work forces, has taken a lead in this field.

In many parts of Africa migrant workers separated from their partners face a combination of poor housing, hazardous working conditions, and serious social disruption leading to alcohol abuse and patterns of sexual behavior that are conducive to the rapid spread of sexually transmitted infections, including HIV/AIDS.<sup>10</sup> In eastern China, migrants with partners were at a relatively low risk for engaging in casual sex.<sup>11</sup> In South Africa, migrant workers and their partners are twice as likely to be infected with HIV as nonmigrant couples.<sup>12</sup> In response to the negative health outcomes that result from isolating migrant workers, and in recognition of the right to family life, many corporations are altering their policies to allow for families to be together in an effort to enhance employee productivity.<sup>9</sup>

The right to health obliges governments to ensure that “health facilities, goods, and services are accessible to all ... without discrimination on any of the prohibited grounds”. In the context of health, these grounds are “race, color, sex, language, religion, political or other opinion, national or social origin, property, birth, physical or mental disability, health status (including HIV/AIDS), sexual orientation, civil, political, social or other status”.<sup>13</sup>

### WOMEN

Women migrant workers are a particularly vulnerable group who may work in unsafe and difficult conditions, encountering violence and abuse both at home and at work. Women are more likely to be trafficked into the sex industry in the host country. The problems faced by female migrant workers, particularly domestic workers, include “withholding of wages, acts of physical and sexual violence, under-nourishment and the seizure of passports”.<sup>14</sup> If found to be HIV positive they may be deported and, on returning to their countries of origin, may experience discrimination, social isolation, and difficulty in finding alternative work. Cases of HIV among domestic workers have been recorded in many migrant-sending countries such as Bangladesh, Indonesia, Philippines, and Sri Lanka and they represent a large percentage of those identified as living with HIV.<sup>15</sup>

### ACCESS AND COMMUNICATION DIFFICULTIES

Migrant workers may not even have the right to access healthcare in their country of work as with the internal migrants. In China, only 19% of rural-to-urban migrants had some form of health insurance and 26% were entitled to limited sick pay.<sup>16</sup> Where healthcare is available, migrant workers may find themselves unable to request time off from work to seek healthcare thus the location, distance, and timing of opening hours of health services may pose problems of access. A crucial element of the right to health is that all health services must be culturally appropriate.

However, these resources are usually limited and require user friendly staff to support and cooperate with migrants to prevent wrong diagnoses, inappropriate treatment, and poor compliance.<sup>17</sup>

Many migrants simply cannot communicate with health providers in a meaningful way. This is more evident in the field of sexual health where communication between the patient and the healthcare provider is of fundamental importance. As a result, the chances of misdiagnosis and inappropriate treatment have been and continue to be high. Only in a few countries are interpreters routinely used in healthcare facilities. Sweden has sought to alleviate this problem, especially in the area of mother and child health where adverse pregnancy outcomes in immigrant groups have proved to be as culturally influenced as they are biologically determined.<sup>18</sup>

## Sexual Health Issues

STIs are a major global cause of morbidity and mortality in migrant adults and children. STIs enhance the transmission of HIV and therefore adequate treatment of STIs is an important component of HIV prevention work worldwide. Antenatal screening for syphilis and HIV is important to prevent congenital syphilis and mother-to-child transmission of HIV.

Economic migrants are likely to be young adults moving alone to large urban centers seeking work. If denied of a stable relationship or family, their sexual needs may be catered for through other routes that may put them at increased risk of infection. Sex industry may develop to cater for their needs and any STI acquired may be transmitted to their partners while on home visits. Migrants have higher risk behavior for acquiring STIs. For instance, central and eastern European male migrants in London have higher rates of partner acquisition and paying for sex while both sexes reported more injecting drug use.<sup>19</sup> In Pakistan only 10% of migrant men reported condom use during the most recent contact with a sex worker.<sup>20</sup>

Migrants are likely to be in a position where they transfer an infection that is highly prevalent in their country of origin into their new host country or they may be moving from an area of low prevalence into an urban area, where the prevalence of STIs is higher. In China, a resurgence of syphilis in urban areas of economic development is driven by the migration of workers from rural areas, purchasing of sex and limited STI knowledge.<sup>21</sup> Furthermore, migrants may acquire STIs while in their host region or country and export them back to their region or country of origin on their return. For example, in Tanzania internal migrants were at a higher risk of HIV infection and contributed to increased rural HIV prevalence.<sup>22</sup>

Particularly vulnerable groups of migrants are the trafficked individuals and undocumented migrants.<sup>2</sup> These people may be moved to a country on the promise of a better life and the ability to send money home to their family. The reality may be a life of exploitation and forced commercial sex work. Their vulnerability and isolation is increased by their illegal status in their host country and consequently they are less likely to utilize formal healthcare services. Furthermore, health education campaigns

tend not to specifically target these groups. Trafficked individuals are more likely to have come from disadvantaged circumstances leading to increased cultural and language barriers and poor knowledge of behavior associated with risk of STIs. Healthcare workers should be aware of local resources available to these individuals and ensure that they are in receipt of ongoing care and support.

## Specific Sexual Health Issues Affecting Migrants

Migrants may import sexually transmitted infections such as HIV, syphilis, and hepatitis B and C infection from countries with a higher prevalence into their host country. Alternatively, they may acquire and transmit globally prevalent STIs such as Chlamydia, gonorrhea, genital warts, and genital herpes in their country of origin or in their host country. The management of these STIs should be identical in both migrants and nonmigrants with relevant investigations and treatment of the individual and their partners in appropriate settings. Other sexual health issues specifically affecting migrants include access to cervical screening programs, sexual assault, sexual dysfunction, and genital mutilation/cutting.

### HIV INFECTION

The HIV/AIDS epidemic appears to have stabilized. The annual number of new infections has fallen since the 1990s and the number of AIDS related deaths is declining due to the provision of antiretroviral medications. Sub-Saharan Africa still bears an inordinate share of the global HIV burden although HIV incidence is falling in 22 countries in the region<sup>23</sup> and this has a significant bearing on the incidence of HIV in their host country.

Immigrants living with HIV have become a strong feature of the epidemiology of HIV in several European countries and the path of migration seems to be influenced by former colonial ties.<sup>24</sup> It is therefore commonplace for people to move, for instance, from Uganda and Zimbabwe to the UK, from The Ivory Coast and The Republic of the Congo to France and from South Africa and Angola to the Netherlands. Sub-Saharan Africa bears 68% of the global HIV burden and therefore migrants from these countries may import HIV infection into their host country.<sup>25,26</sup> HIV risk may continue after migration as a result of sexual mixing patterns within the at risk communities or because of travel back to high incidence areas. Within Africa also migrant workers are a risk group for HIV infection.<sup>27</sup>

Data from UK in 2010 shows that 60% of the persons infected heterosexually were of black-African ethnicity and 70% acquired their infection abroad. Among those heterosexuals infected abroad, the majority have acquired their infection in sub-Saharan Africa. The number of heterosexually acquired HIV cases in people born in Asia, Latin America, and the Caribbean is also increasing reflecting both migration patterns and global HIV epidemiology. The number of deaths in black Afro-Caribbean individuals with HIV infection accounted for almost 30% of



all HIV related deaths; this may be related to late diagnosis or in some cases to not starting antiretroviral therapy at the appropriate time. Under diagnosis of HIV is more common among non-UK born people than among the UK born which raises questions about the adequate awareness of risk in non-UK born communities or a perceived stigma regarding testing and their onward entitlement to hospital services.<sup>28,29</sup>

HIV can be associated with stigma in many communities and this can be a barrier to seeking help which could delay diagnosis. Addressing stigma requires culturally appropriate approaches with the affected groups as well as education of the wider population. The general public needs to be reassured that they cannot acquire HIV through normal social contact with affected individuals. This will help to avoid the misconception that migrants pose a health threat to the general population which can lead to prejudice that is likely to hinder overall HIV control.

## SYPHILIS

Syphilis is an entirely treatable sexually transmitted infection but with an estimated 12 million people infected each year it remains a global problem.<sup>30</sup> Expectant mothers infected with syphilis can transmit the infection to their unborn child and despite national policies on antenatal testing more than 1 million infants are born with congenital syphilis each year.<sup>31</sup> China is experiencing a resurgence of acquired and congenital syphilis, especially in their migrating population.<sup>32,33</sup> Similarly it has been shown that male migrants returning to Nepal from Mumbai have high rates of syphilis infection after engaging in pre- or extra marital sex, sex with multiple partners including sex workers.<sup>34</sup> Outbreaks of syphilis in central and eastern Europe and Russia were reflected in women and female sex workers from these countries living or working in their host countries in western Europe.<sup>35–37</sup>

Part of the difficulty experienced with syphilis screening and testing is that traditional serological testing relies on availability and the patients returning for their results, which can be a problem for migrants in particular. The development of a new robust rapid specific test provides an opportunity to scale up syphilis screening in many settings.<sup>38</sup>

## HEPATITIS B AND HEPATITIS C INFECTION

Viral hepatitis B and C are a major health problem worldwide. Migration of individuals with chronic viral hepatitis infection substantially contributes to the prevalence of these infections in low-endemic countries.<sup>39–43</sup>

Both chronic hepatitis B and hepatitis C can cause cirrhosis and hepatocellular carcinoma (HCC). The epidemiology of HCC is therefore changing as a result of migration and host countries of individuals from highly endemic areas are observing increases in their incidence of HCC.<sup>44</sup> Many of the migrants with chronic hepatitis B infection will have acquired their infection at an early age, hence hepatitis B vaccination policies will be unable to protect the already infected migrants from the sequelae of hepatitis B infection. For this group diagnosis and treatment may, however,

contribute to reducing the impact of the infection on their individual health, and awareness of the disease can prevent transmission to others, particularly transmission to babies from their mothers. Treatment for chronic hepatitis B has improved and new drugs for the treatment of hepatitis C are on the horizon. Efforts should therefore be made to identify individuals in order that treatment can be offered preventing long term complications. Screening programs targeting migrants from endemic countries that could be implemented are population based screening, opportunistic testing, or enhanced contact tracing.<sup>45</sup> Universal hepatitis B vaccination as recommended by the WHO in all infant vaccination programs worldwide<sup>46</sup> is essential to prevent transmission in the uninfected and the population at large as targeted vaccination programs to high risk groups are not effective.<sup>47</sup> Failure to implement universal vaccination affects migrants from hepatitis B endemic area and their family and sexual partners disproportionately. In rural Vietnam, out-migration of the husband was associated with an increased risk of hepatitis B surface antigen seropositivity among married women.<sup>48</sup>

## CERVICAL CANCER AND SCREENING PROGRAMS

Access to a cervical cancer screening test to prevent cervical cancer should be available to all.<sup>49</sup> Geographic variations in the risk of developing cervical cancer are associated with variation in the occurrence rate of oncogenic human papillomavirus (HPV) around the world, smoking rates, sexual habits, and the availability of screening tests.<sup>50</sup> The variability in the cervical cancer rates between the migrant women depends on their country of origin and the variability of the above stated risk factors. Increased rates have been observed in women migrating from Poland and Bosnia,<sup>51</sup> Norway, Denmark and Central America<sup>50</sup> and internal Spanish migrants.<sup>52</sup> Lower rates of cervical cancer have been observed in women originally from Iran, Iraq, and Finland<sup>51</sup> and southern Asia and east Africa.<sup>50</sup> Evidence from Canada, Australia, and New Zealand reinforces lower uptake of cervical cancer screening among migrant women compared with their native counterparts.<sup>53–55</sup> Increasing age at the point of migration has also been noted as a risk factor for cervical cancer.<sup>50</sup> It is important to understand the disparities in healthcare suffered by migrant women compared with nonmigrants.<sup>56</sup> Culturally sensitive cancer prevention programs should focus on individual risk patterns and high risk women, especially older women who have recently migrated, should be targeted.

## SEXUAL DYSFUNCTION

Sexual dysfunction is a common complaint in both male and female migrants attending sexual health clinics. Premature ejaculation is more common in migrants from the Indian subcontinent particularly Islamic men.<sup>57</sup> Factors associated with premature (rapid) ejaculation in men included: anxious first sexual experience (associated with a fear of being discovered and wanting to finish early), sex before marriage, sex outside of marriage, religion,

“stress,” and exposure to Western images. These factors have useful therapeutic implications when counseling men with premature ejaculation but may also be reflective of sexual dysfunction with alternative presentations. Treatment of premature ejaculation using masturbatory techniques may not be acceptable to many migrants with strong cultural and religious beliefs and so other methods of treatment may be required. When discussing sexual dysfunction it is important to understand cultural relativism and that the healthcare provider’s view of “normal” sexual behavior is perhaps not the same as that of their patient.<sup>58–61</sup>

## **RAPE/SEXUAL ASSAULT**

Rape has been a common feature of many armed conflicts around the world. Women in such circumstances may be internally displaced or choose to migrate, seeking asylum abroad. Aside from the physical and psychological distress felt by the individual, women are often rejected by their family or community because of the shame rape brings. Sexually assaulted women are also at risk of acquiring STIs including HIV. The war in former Yugoslavia increased all forms of violence against women including domestic violence, particularly in inter-ethnic marriages, death threats against women, rape and threats with weapons. In Rwanda, there were reports of women being gang-raped and sexually mutilated; fathers forced to rape their daughters; and sons their mothers.<sup>62</sup> The UN Security Council specifically included sexual violence against women as a weapon of war.<sup>63</sup>

Rape victims who are displaced or are seeking refuge in another country will therefore need health services to be aware of the problem and will need culturally appropriate psychological and physical support. As a minimum, good practice will ensure that women are offered a suitable appointment with a minimal waiting time and private waiting area for use if the patient is distressed. An independent translator should be provided and onward links with the relevant and other support agencies ensured.

## **FEMALE GENITAL MUTILATION OR CUTTING**

Female genital mutilation (FGM) refers to all procedures involving partial or total removal of the external female genitalia, or other injury to the female genital organs for nonmedical reasons. The term ‘female genital cutting’ reflects the use of a nonjudgemental terminology with practising communities. In African countries, more than 90 million girls and women over the age of 10 years are estimated to have undergone FGM, and some 3 million girls are at risk of undergoing the procedure each year. The practice of FGM has been reported from all parts of the world, but it is most prevalent in 28 countries in Africa and some countries in Asia and the Middle East. As a result of international migration, the practice of FGM and its harmful consequences is a concern for a growing number of women and girls in Europe, North America, Australia, and New Zealand.<sup>64</sup>

This practice is a violation of girls’ and women’s human rights and is illegal in many areas of the world. FGM is known to be harmful in many ways as it involves the removal of healthy genital

tissue, interferes with the natural functioning of the body, and causes several immediate and long-term physical, psychological, and sexual consequences. Despite there being evidence to support the occurrence of primary infertility after genital mutilation, families and individuals continue to perform it because they believe that their community expects them to do so. They suspect that if they do not respect the social rule, they will suffer social consequences such as derision, marginalization, and loss of status.<sup>65</sup>

## **Vulnerable Groups**

Aside from a higher rate of infections within certain populations, migrants may face compounding factors on arrival in their host country which further increase their risk for acquiring STIs/HIV.

## **DRUG AND ALCOHOL USERS**

Recreational drug use is associated with increased sexual risk taking and intravenous drug users are more at risk from blood borne virus infections. After a period of drug control in China there is evidence of an increase in illicit drug use in internal male migrants. Depression and earning a higher income were positively associated with drug use.<sup>66</sup> Drug users who move country may find themselves further marginalized due to language barriers and difficulty with access to healthcare. Italian intravenous drug users living in Amsterdam reported a high prevalence of needle borrowing, needle lending, and HIV infection.<sup>67</sup> A pan-European survey of undocumented migrants carried out by Médecins du Monde revealed that the prevalence of drug abuse in this group and in the under-25s population was approximately 5% and 9%, respectively. Prevalences varied by country with nearly 20% prevalence in Italy.<sup>68</sup> Among male Hispanic/Latino migrant farm workers in Southeast USA, 40% who reported sex during the past 3 months performed it under the influence of alcohol.<sup>69</sup> Outreach work is needed with this population to educate them regarding risk reduction and so decrease onward transmission of infections. Close links with local substance misuse services are beneficial.

## **COMMERCIAL SEX WORKERS**

In many countries in Europe, the majority of sex working population is made up of foreigners. In countries where commercial sex is legalized and commercial sex workers (CSWs) have been registered, unregistered sex workers, many of whom will be migrants, may even outnumber the registered CSWs.<sup>70</sup>

Sex workers from eastern Europe working in western European countries had a higher prevalence of syphilis and little knowledge of STD risks or effective contraceptive use.<sup>32</sup> Street based sex workers in East London showed high rates of drug use (92%), a high prevalence of syphilis (58%) and that 28% of them were non-UK born.<sup>71</sup> Work with internal economic migrant female sex workers from China on their barriers to condom use and subsequent HIV risk showed that their use of condoms was influenced by gender norms, familiarity, and whether more money was offered.<sup>72</sup>

In a population of migrant sex workers in Spain, 5.2% had antibodies to HIV-1, 3.5% tested positive for HBsAg, and 3% were positive for syphilis antibodies. However 28.6% of Ecuadorians had active syphilis and all HIV-1 positive in this group were transsexual men.<sup>73</sup>

Female sex workers in the US Virgin Islands using illicit drugs were significantly more likely to report unprotected sexual activity, client violence, and sexually transmitted infections. This group of women also engaged in sex work in a significantly greater number of countries and were more likely to work in locations outside the US Virgin Islands.<sup>74</sup>

Targeted work is needed with this cohort to ensure the availability of sex education regarding infection prevention and contraception. Services should have links to drug-dependency units and have facilities to support women, should they choose to continue working in the sex industry or not. Clients also need to be educated on safer sex. For instance, a behavioral survey of migrant taxi drivers in Bangladesh showed that 64% of the sample reported sex with multiple commercial sex partners and only 5.6% used condoms consistently. It indicates that not only CSWs but also migrant men who are likely to be their clients need to be a target for intervention.<sup>75</sup>

### MEN WHO HAVE SEX WITH MEN (MSM)

A further vulnerable group are the black and minority ethnic (BME) men who have sex with men (MSM) population. MSM migrants from the Caribbean, Africa, South Asia (India, Pakistan, Bangladesh, or Sri Lanka) and China/South-East Asia (Malaysia, Thailand, Philippines) and Japan have been shown to be more likely to report unprotected anal intercourse with casual male partners and also likely to report female sexual partners.<sup>76</sup> Seventy-two percent of young migrant MSM in Beijing, China had never had an HIV test. Barriers to testing included perceived low risk of HIV infection, stigmatization, inconvenience of testing, and lack of confidentiality while HIV testing behavior was associated with increased high risk sexual behavior and a history of sexually transmitted infections.<sup>77</sup> In the United States, BME MSM bear a disproportionate burden of incident HIV; among young BME MSM surveyed in 6 US cities between 1994 and 2000, the HIV incidence was 14.7% compared to 2.5% among white MSM.<sup>78</sup> High rates of bacterial STIs and risky sexual behaviors among black minority ethnic groups, compounded by racism and cultural taboos surrounding sexual orientation, mean that we must remain alert to the sexual health needs and evolving epidemiology of HIV among BME MSM. Furthermore, BME MSM may be marginalized by the BME community and by the MSM community and therefore appropriate and culturally specific sexual health services should be planned.<sup>79,80</sup>

### Actions Required

International and Governmental bodies and agencies need to work together to ensure that migrants have proper safeguard, protection, and provision of appropriate health services.

Many health systems are based on Western medical knowledge and practices. Health policies assume that migrants will adopt the health practices and beliefs of the host society. However, the access and the use of health services can be obstructed by differences in health beliefs and knowledge. National health services need to invest in overcoming the language barrier and training health service providers to identify migrants at risk of STIs and HIV and ensure acceptability of their service to these individuals. Health service providers need to be informed about the cultural background and particular barriers that different types of migrants in different situations may face. Migrants' participation in health service provision will improve the accessibility of these services for migrant communities. The understanding of different medical traditions will enhance the cultural appropriateness of health and social services.

Migrants should be provided with information on the health services that are available for their use. Outreach work can facilitate and integrate targeted STI prevention measures into education programs. Often migrants are neither included in the development of migrant services nor asked for feedback on these services. Thus, many services are not used because they are not culturally acceptable to migrants. A study in Switzerland has shown that female migrants' lack of awareness of healthcare and preventative services has been a major reason why they have been underutilized.<sup>81</sup> They identified a need for culturally and linguistically appropriate education on contraception, family planning, and cancer screening. Lessons can be learnt from the Swedes who, in their National Action Plan for STI/HIV prevention, suggest that targeted information about STIs and HIV should be provided to persons recently arriving in Sweden.<sup>82</sup> An important strategy in reducing the spread of HIV is to look at measures to integrate new Swedes into their society. Therefore, efforts should be made to counteract discrimination, xenophobia, and racialism to improve society's attitudes to minority groups, particularly homosexuals and migrants from Africa and Asia. The fact that many of the groups targeted for information about HIV and AIDS have experienced discrimination in their country of origin instinctively increases their reluctance to accept messages from the host society.

### Conclusion

Migrants are an extremely heterogeneous group and coping with cultural, social, and psychological effects of migration is a very difficult and prolonged adaptation process. The management of migrants' sexual health goes beyond the traditional management of diseases among mobile populations and is intrinsically linked with the broader social-determinants of health and unequal distribution of healthcare and social services. It is therefore paramount that different disciplines work in close partnership to avoid social exclusion and improve the health of all people including migrants. Therefore, work on facilitating social and economic integration of migrants is vital. If we can promote a greater understanding of the needs of the migrants and encourage a charitable attitude among the indigenous population of their



host country we will ensure that helping migrants does not undermine helping the locally underprivileged. Integrating migrants into society can enrich their host country both culturally and economically.

### Summary

- Migrants are a heterogeneous group with different needs.
- Sexual healthcare should be provided to migrants regardless of their legal status.
- Healthcare services should be culturally appropriate with access to interpreters.
- Specific infections prevalent in the individual's country of origin must be considered.
- Some knowledge about their sexual practices, cultural values, traditions, and taboos will be helpful.
- Particularly vulnerable groups of migrants should be identified for targeted STI prevention work.
- Efforts need to be made to counteract discrimination of migrants and to integrate them into their host society.

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# section **xiv**

## **HUMAN SEXUALITY, SEXUAL ORIENTATION, AND SPECIAL ISSUES**

— *Darren Russell*

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## Introduction

In everyday life, the word “sex” is often used to mean male or female (biological gender) or to refer to physical activity involving the genitals (having sex). The word “sexuality” has a broader meaning. Sexuality means a dimension of personality instead of referring to a person’s capacity for erotic response alone.<sup>1</sup> Human sexuality is defined as that aspect of the human condition, which is manifested as sexual desire, appetite, associated physiological response patterns, and behavior which leads to orgasm, or at least pleasurable arousal, often between two people, but not infrequently by an individual alone.<sup>2</sup>

It will be scientific to use the word “sexuality” as it is holistic and refers to the person as a whole including his/her thoughts, experiences, learnings, values by virtue of being male or a female.<sup>3</sup>

## Human Sexual Response Cycle and Sexual Dysfunctions

Consequent to direct observation of 10,000 live sexual cycles, it was in 1966, Masters and Johnson first described the four stage model of the normal human response cycle, in their classic book, “Human Sexual Response.”<sup>4</sup> Human sexual response cycle consists of: Excitement Phase, Plateau Phase, Orgasm and Resolution Phase. Kaplan added “Sexual Desire” to the classical four stage model.<sup>5</sup> Subsequently, in 1970, the famous couple, Masters and Johnson used the term “sexual dysfunction”<sup>6</sup> principally intending to convey psychological malfunctioning; at that time most sexual dysfunctions were considered psychogenic. Based on the ideas of Masters and Johnson and Kaplan, in 1980, the concept of “Psychosexual Dysfunction” appeared in the third edition of Diagnostic and Statistical Manual of Mental Disorders (DSM) of American Psychiatric Association.<sup>7</sup> The current DSM-IV classification (American Psychiatric Association 2000) defines sexual dysfunction as characterized by disturbance in sexual desire and in the psycho-physiological changes that characterize the sexual response cycle, causing marked distress and interpersonal difficulty.<sup>8</sup> Following are the definitions given in DSM-IV (Text revised):

### 1) Sexual desire disorders

- **Hypoactive sexual desire disorder (HSDD):** Persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. The judgment of deficiency or absence is made by the clinician, taking into account factors that affect sexual functioning, such as age and the context of the person’s life.
- **Sexual aversion disorder:** Persistent or recurrent extreme aversion to, and avoidance of, all (or almost all) genital sexual contact with a sexual partner.

### 2) Sexual arousal disorders

- **Male erectile disorder (erectile dysfunction [ED], impotence):** Persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate erection.
- **Female sexual arousal disorder (FSAD):** Persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement.

### 3) Orgasmic disorders

- **Premature ejaculation (only in men):** Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity. (This definition is not universally accepted; some definitions include a specific time limit of one or two minutes between vaginal penetration and ejaculation.)
- **Male orgasmic disorder:** Persistent or recurrent delay in, or absence of orgasm following a normal sexual excitement phase. The clinicians should take into account the patient’s age and whether the stimulation is adequate in focus, intensity, and duration.
- **Female orgasmic disorder:** Persistent or recurrent delay in, or absence of, orgasm following a normal sexual

excitement phase. Women exhibit wide variability in the type or intensity of stimulation that triggers orgasm. The diagnosis of female orgasmic disorder should be based on the clinician's judgment that the woman's orgasmic capacity is less than would be reasonable for her age, sexual experience, and the adequacy of sexual stimulation she receives.

#### 4) Sexual pain disorders

- **Dyspareunia (both in men and women):** Recurrent or persistent genital pain associated with sexual intercourse in either a male or a female.
- **Vaginismus (only in women):** Recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with sexual intercourse.

According to DSM-IV, to be defined as a "dysfunction" these disorders must also cause marked distress or interpersonal difficulty, and not just exclusive presence of the general medical condition.

#### PERSISTENT GENITAL AROUSAL DISORDER (PGAD)

This is a rare condition and was first reported recently by Leiblum & Nathan.<sup>9</sup> Almost all reported cases have been in women. It can be identified by the following descriptive features:

Genital and breast vasocongestion persisting for hours or days, which resolves only temporarily following orgasm and may require multiple orgasms to get relief. The feeling of genital response, is not associated with any sense of sexual desire or excitement, is intrusive and disturbing and can be triggered by a variety of non-sexual stimuli. No consistent cause has been identified for this condition. Even though several hypotheses are proposed, none had been proved. There is also lack of evidence-based data regarding the prevalence of PGAD and the condition is not mentioned in DSM-IV.

#### Epidemiology of Sexual Dysfunctions

**Erectile dysfunction:** In the recent years, many studies on prevalence of erectile dysfunction have been published, but the conclusions vary significantly. A review of 15 large scale prevalence studies from 1994 to 2004, reporting men with erectile dysfunction as a percent of the studied population shows that the prevalence of ED varied from a low of 10.2% in Laumann's US study of men aged between 18 and 59 years, to a high of 64% in Akkus' Turkish study of men over 40.<sup>10–17</sup> The most popular Massachusetts male aging study demonstrated an overall prevalence of 52% in men aged 40–70.<sup>11</sup>

**Premature ejaculation (PME)** is one of the most common male sexual dysfunctions, affecting 5–40% of sexually active men.<sup>18</sup> It is believed that there is a higher frequency of PME in adolescents or young adults. PME is most frequently reported by men in East Asia and less frequently by men in Middle Eastern and African countries. The European prevalence of PME is said to be between that of East Asia and Middle East and African countries.<sup>19</sup>

A recent European survey of 2467 women in France, UK, Germany, and Italy indicates that the percentage of women with low sexual desire is 16% in the age cohort from 20 to 49; 29% in the same age cohort in women who experienced surgical menopause; 42% in postmenopausal women aged 50–70 with natural menopause and 46% in the same age cohort after surgical menopause.<sup>20</sup>

**Sexual aversion disorder in women** is frequently a component of other diagnostic disorders, especially anxiety-based disorders.<sup>10</sup> In a study done by Hutchings and Dutton, it had been concluded that 75% of sexually abused women had anxiety disorders as compared to 21% of non-abused women with anxiety disorders.<sup>21</sup> Another study by Dinwiddie et al.<sup>22</sup> demonstrated the increased incidence rates of psychopathologies in those twins who were sexually abused as compared to those twins who were not abused. This shows a strong correlation between childhood trauma or sexual abuse and incidence of panic disorders.<sup>22–24</sup> This hypothesis was initially linked to sexual aversion disorder by Kaplan<sup>25</sup> in her discussion on clinical perspectives of intimacy and panic disorders.

The epidemiological data on **female sexual arousal disorder (FSAD)** show a wide range of prevalence, based on the study methods adopted and the definitions used in the study. The overall prevalence rates are between 6% and 49%<sup>13,26–32</sup>. Two studies concluded that the prevalence of FSAD is increasing with increasing age, peaking after the age of 50 years.<sup>30,31</sup>

#### Sexually Transmitted Infections and Sexuality

It is a depressing reality that one can get a disease from making love. And yet, STIs are a very real concern. Probably STIs are the most prevalent infectious diseases next to the common cold; hence, the need for a discussion on sexuality in a textbook on STIs.

It is important to keep one distinction in mind. One does not get an STI because he/she has sex. Rather, one contracts an STI through sexual contact with an infected person. For suppression of sexual activity, moralists have long used the idea that an STI is one of the penalties of sex. It is an old and tenacious fallacy. STIs occur as a result of ignorance and lack of sexual responsibility. It is the consequence of failure to plan sexual activities and to take responsibility for sexual behaviors.<sup>32</sup> Sexual abstinence as a preventive means against STIs is not the answer. The answer is to be aware of preventing, detecting, and treating STIs so that they do not interfere with a person's life and sexual functioning.

It is important to realize that the sexual urges and practices of human beings are unlikely to be inhibited by the threat of severe pain, complete disability and even death, including the morbidity which may result from sexually transmitted infections. If it was so, STIs would have been eradicated long ago. In spite of the AIDS scare, extramarital sex has not disappeared.<sup>33</sup>

Because of this recent epidemic of AIDS, interest in human sexual behavior and the factors influencing it has acquired enormous significance.

## FACTORS INFLUENCING SEXUAL BEHAVIOR

As with virtually all aspects of human behavior, there are elaborate laws and codes of morality, both written and unwritten, which govern sexual relations/acts/behaviors. It is unfortunate that many of these are based on taboos and superstitions, and above all ignorance.<sup>34</sup>

It may be surmised that when human beings were evolving, their survival was by no means certain, and thus a very high reproductive rate was a great advantage. It seems possible that many elaborate cultural and social patterns which have evolved around the act of sex are a result of that original basic biological need to procreate as much as possible.<sup>34</sup>

Today humans are no longer in danger of under reproducing but rather over reproducing. Consequently, the primary focus of human sexuality, namely procreation, is being replaced with other foci of sexuality like recreation and relation. Naturally these new needs will have to be governed by a new set of moral codes. Unfortunately while moral codes are rapidly changing, superstitions and ignorance are not changing. They continue to cling tenaciously in the minds of not only the non-medical persons but also the medical fraternity.

The belief that humans indulge in sex only for the sake of sexual pleasure is no more tenable. Sorenson<sup>35</sup> had identified a variety of reasons other than sexual pleasure, which make people to be sexually active. Any healthcare professional has to necessarily understand all these in order to be able to manage people who come to him/her with sexual problems and problematic sexual behavior.

Human beings may be described as learning animals. However, unlike other animals human beings are sexually excited by different kinds of sexual stimulation and circumstances. This excitatory process is largely learned, and the various types of responses to individual stimuli and situations depend on the individual's past experience.

These learning procedures may be, and often are, purely trial and error, but by far the greater part are learned from other people and within the general social context in which the individual is brought up and lives. Thus, in addition to being learning animals, humans are also social animals. As a result their sexual behavior is inevitably channeled into certain patterns consistent with their particular cultural backgrounds. From this evolving culture the individual will learn right from wrong, various codes of conduct, and how, when, and where to behave in certain ways. These codes and behaviors may, of course, be quite different for men and women, and even between social strata within the same society. But whatever the differences, every individual will be subject to strong pressures to conform to the traditional sexual behavior patterns accumulated through hundreds, and perhaps thousands, of years of cultural heritage.

Human sexual behavior then, must be viewed with these three things in mind; the purely biological factors, the learning processes, and the sociocultural environment. Since large cultural variations exist between different groups of

people throughout the world, it is not surprising to find, as anthropologists have amply demonstrated, large variations in sexual behavior in various civilizations all over the world.

## PREMARITAL SEX

Ford and Beach<sup>36</sup> divided societies into three types, while reviewing the sexual behaviors:

1. Restrictive societies in which sexuality outside marriage was generally discouraged.
2. Semi-restrictive societies with formal prohibitions but not enforced with any vigor. Sexual behavior among the unmarried was accepted provided it was in secret, but if pregnancy ensued, marriage was expected.
3. Permissive societies; in some cases the permissiveness applied to early childhood only, but often continued at least until marriage. Sexual activity between young people was expected, but once again, the occurrence of pregnancy was seen as an indication for marriage.

Broude and Greene<sup>37</sup> in human relations area file (HRAF) reported that premarital sexual activity is not common for females in 43% and for males in 31% of the 141 societies they studied. Whyte<sup>38</sup> felt that a double standard exists for premarital sexuality in 44% of the societies surveyed.

## SOURCES OF INFORMATION

There are three important sources of information: (i) historical evidence of changing patterns of sexual behavior; (ii) cross-cultural anthropological studies of primitive societies; and (iii) surveys of sexual behavior and attitudes in modern societies.

It is important to recognize that none of these sources are foolproof and are as susceptible to bias as any other source of information. However, it must be acknowledged that these sources are valuable in the sense that they are indicators or guidelines of sexual behavior of large ethnic groups.

While anthropological data are a rich source, few anthropological studies have focused on sexuality.<sup>39–41</sup> Since the past 50 years more than 50 surveys on the sexual behavioral patterns of the western society have been conducted. Unfortunately their value is very variable. Standing out from others in terms of size and importance are the Kinsey reports.<sup>42–44</sup>

While some surveys concentrated on the behavior alone, others concentrated on attitudes in addition.

In spite of the difficulties in obtaining representative population samples, there is much to be gained by surveying sexual behavior. They are useful in: (i) establishing norms for comparative purposes, (ii) policy making in education and health, (iii) challenging false myths, (iv) changing social attitudes, and (v) testing hypotheses about relationships between sexuality and other variables.<sup>45</sup>



## SEXUAL NORMALITY

A tendency in medical writing on sexuality is to regard certain forms of sexual behavior as either normal or pathological. This categorization makes the medical personnel difficult to understand the concerns of an individual who seeks medical help, e.g., homosexuals. While some of the so-called “pathological” individuals may seek help, others may not, even though they can be (mistakenly) considered to be “pathological.” These individuals do not seek help to “cure” their condition.

Attitudes to sexual behavior are so very emotive and hence any behavior that is not regarded as normal will tend to be seen as abnormal in a derogatory way.

There are many concerns regarding sexuality. Perhaps the biggest and most vexing of all is: “Am I normal?” Almost every human being has this doubt at some point in his/her life, in relation to sexual development, sexual practices, feelings, and desires. Unfortunately, there are no definitive answers to these bothersome questions. The most appropriate answer will be “it depends.” It depends upon the context in the individual’s life. So, how is one to assess normality? Wardell Pomeroy<sup>46</sup> was of the opinion that there are multiple standards to assess normality: statistical, religious/moral, and psychological/sociological.

From a sociological perspective behavior that falls outside the accepted customs and rules of a particular society is deviant. The psychological perspective stresses that anything that produces a subjective sense of distress is abnormal. Statistically, normality becomes a matter of numbers. If a particular type of sexual behavior is frowned upon by a significant segment of the population, then it becomes abnormal. Similarly what is frowned upon by a significant religious group is abnormal. Michael Carrera<sup>47</sup> adds two more standards, namely, legal and phylogenetic. The legal perspective is that anything which violates the law is abnormal. The phylogenetic (biological) viewpoint of normality implies healthy against diseased. While each standard appears to be definitive from its perspective, they all have their own exceptions. To conclude, no one standard is comprehensive. Sexual behavior is culturally and religiously relative. Standards of sexual behavior vary with time and place. Scientific research, by giving us clearer view of what actually happens can alter our views.

The best and most realistic criteria for judging if a particular sexual practice is acceptable or not is whether it is harmful in some way to either oneself or the partner. It is indisputable that one cannot do oneself good by harming others. STIs greatly enlarge the possibility of harming others through sex or being harmed by them. However, the ethics governing our attitudes towards STIs need not be different from ethics of sexuality in general. Behavior that is based on awareness, caring, compassion, and responsibility will serve well.

## CONCEPT OF SEXUAL DEVIANCE

Deviance is a behavior that contravenes the norms of society. These norms combine the institutionalized norms or laws and the internalized and shared norms or mores. Deviance is sometimes

defined in terms of statistical abnormality or of psychopathology. The statistical criterion tells us nothing of the value or the problems associated with a particular form of behavior. The criteria used to define psychopathology may be no more than medical rationalization of the social criteria. A typical example of this is homosexuality. The sociological definition is however valid and important as it confronts us with the social stigma, which plays such important negative role in the lives of “deviant” individuals. Unfortunately, the term deviant has grown to have pejorative connotations, so that when using it one may be accused of expressing a negative value about the particular behavior or individual. This is unfortunate as the concept of deviance is essential to our proper understanding of the plight of these individuals in society.

Gagon et al.<sup>48</sup> drew an important distinction between three types of sexual deviance. The first they called “normal deviance,” this encompasses behaviors such as masturbation, premarital sex, and oral-genital sex. These activities are frowned upon in some parts of the world even today and are legally proscribed. These behaviors, nevertheless carried out by large number of people, are becoming progressively destigmatized. The other two types of deviance distinguish between behaviors which are associated with particular subcultures (such as homosexual subcultures) called subcultural deviances and those which are not (such as exhibitionism or incest). The later group is known as “individual deviance.” The existence of a sub-culture with which the deviant individual can identify may be crucial to his wellbeing and adaptation. This helps the concerned individual to have a social group in which he feels normal. Otherwise he will always feel abnormal and stigmatized. Such sub-cultures are never static. They are constantly evolving and changing, reflecting the changing attitudes of the societies. In the mid 19th century, homosexuals had no homosexual subculture. Now there is an international network of such organizations. All homosexuals may not identify with these groups and may remain isolated. But the option is there now. Other types of “deviant” sexuality have generated their own organizations or sub-cultures. There are now well-established organizations of transvestites and trans-sexuals, and to a lesser extent of fetishists and sadomasochists.

## LABELING AND STIGMATIZATION

Using words like “normal” or “abnormal” to describe behavioral patterns may sound scientific or official. This is called “labeling.”<sup>49</sup> Labels affect how an individual views others and in turn how others view the individual.

The negative effects produced by labeling are known as “stigmatization.” It brands people as undesirable with social, legal, and economic consequences. In order to avoid the stigmatization caused by labeling, the word “paraphilia” has been suggested to refer to those behaviors which were known as “perversions” or “deviations.”

## Paraphilias

The word paraphilia is from Greek roots “para” and “philia” meaning “altered” and “love.” Currently, they are classified as

psychiatric disorders. In the third revised edition of diagnostic and statistical manual (DSM-III) of the American Psychiatric Association<sup>50</sup> the legal term perversion was dropped and the biomedical term paraphilia was adopted.

By far the most comprehensive definition of paraphilia is given by Money.<sup>51</sup> He defines paraphilia as “a condition occurring in men and women of being compulsively responsive to, and for optimal initiation and maintenance of sexuorotic arousal and the facilitation or attainment of orgasm, obligatively fixated and dependent on an unusual, personally or socially unacceptable stimulus either perceived directly, or in the imagery or ideation of fantasy.”

A paraphilia can revolve around a particular sexual object (e.g., children, animals, underwear) or a particular sexual act (e.g. inflicting pain, making obscene phone calls).<sup>49</sup>

Money<sup>52</sup> described fifty-two types of paraphilic sexual behaviors ranging from “acrotomophilia” (amputee partner) to “zoophilia” (sex with animals).

Most paraphilias involve sexual acts that violate the law in one form or another. For example, exhibitionism comes under laws against “indecent exposure.” Voyeurism falls under “an unwanted invasion of privacy.” Sadistic acts may violate laws on assault.

Hence, paraphilics are in a state of limbo in a legal sense. Often paraphilics are categorized as “sexual psychopaths,” a term that is not a psychiatric diagnosis but a legal label. This designation permits the society to impose an indeterminate punishment and also to dub them as a menace to society. While this may be true of some paraphilics, it is difficult to see how someone like a transvestite is a menace or danger to the society.

The issue being so, how to determine which paraphilias are pathological and which are not, at least in a legal sense. The laws of many countries declare by fiat which paraphilia, if enacted, are criminal offences. Such paraphilias were called “crime against nature” because they break what was assumed to be God’s natural law. In these instances, the natural law is specified as “God’s natural law of procreation.” In recent times, however, some law agencies are handing over these “crimes against nature” to medical fraternity, so that they can be reclassified as illnesses instead of crimes.

Money distinguishes between benign acts that do not harm others and pathological acts, which harms others by utilizing the concept of mutual consent.<sup>53</sup>

As of today there is no general agreement on the etiology of paraphilias. A variety of factors have been postulated to cause paraphilias. These can be broadly classified into biological, cognitive behavioral, and psychodynamic. Prenatal developmental anomalies,<sup>54</sup> increased testosterone levels,<sup>54</sup> organic brain disorders,<sup>55</sup> obsessive-compulsive disorders<sup>56</sup> are among the cited biological factors. Behavior therapists suggest that paraphilias begin via a process of conditioning.<sup>57</sup> Psychoanalytic theory is that these conditions represent “a regression to or a fixation at an earlier level of psychosexual development resulting in a repetitive pattern of sexual behavior that is not mature in its application and expression.”<sup>58</sup> Money proposed the “vandalized love map” theory to explain paraphilic behavior.<sup>59</sup>

The American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), the prevailing resource for diagnostic criteria of paraphilias, describes the essential feature of paraphilias as recurrent, intense, sexual urges, and sexually arousing fantasies generally involving non-human objects, the suffering or humiliation of oneself or partner, or children or other non-consenting persons.<sup>8</sup> The DSM-IV-TR lists the following paraphilias: exhibitionism, fetishism, frotteurism, pedophilia, sexual masochism, sexual sadism, transvestic fetishism, voyeurism, paraphilias NOS (not otherwise specified).

### **Exhibitionism**

Exhibitionism is the exposure of genitals to a non-consenting stranger. In some cases, the individual may also engage in autoeroticism while exposing himself. Generally, no additional contact with the observer is sought; the individual is stimulated sexually by gaining the attention of and startling the observer.

### **Fetishism**

People with this disorder achieve sexual gratification with the use of objects, most commonly women’s under-garments, shoes, stockings, or other clothing items.

### **Frotteurism**

Individuals with this disorder are gratified by touching or rubbing a non-consenting person. This behavior often occurs in busy, crowded places, such as on busy streets or on crowded buses or subways.

### **Pedophilia**

Pedophilia involves sexual activity with a child, generally under age 13. The DSM-IV-TR describes a criterion that the individual with pedophilia be over 16 years of age and be at least 5 years older than the child. Individuals with this disorder may be attracted to either males or females or both, although incidents of pedophilic activity are almost twice as likely to be repeated by those individuals attracted to males. Individuals with this disorder develop procedures and strategies for gaining access to and trust of children.

### **Sexual Masochism**

Masochism is a term applied to a specific sexual disorder but which also has a broader usage. The sexual disorder involves pleasure and excitement produced by pain, either inflicted by others or by oneself. It usually begins in childhood or adolescence and is chronic. An individual with this disorder achieves gratification by experiencing pain. The term comes from the name of a 19th century Austrian writer, Leopold von Sacher-Masoch, whose novels often included characters who were obsessed with the combination of sex and pain.

In the broader sense, masochism refers to any experience of receiving pleasure or satisfaction from suffering pain. The psychoanalytic view is that masochism is aggression turned inward, onto the self, when a person feels too guilty or is afraid to express it outwardly.

### Sexual Sadism

A sadistic individual achieves sexual gratification by inflicting pain on another person.

The disorder was named after Marquis de Sade, an 18th century French author and military officer who was repeatedly imprisoned for his violent sexual acts against women. In psychoanalytic theory, sadism is related to the fear of castration, while the behaviorist explanation of sadomasochism (the deviant sexual practice combining sadism and masochism) is that its constituent feelings are physiologically similar to sexual arousal. Separate but parallel descriptions are given for sexual sadism and sexual masochism in the DSM-IV-TR. The clinical diagnostic criteria for both are recurrence of the behavior over a period of at least 6 months, and significant distress or impairment of the ability to function as a result of the behavior or associated urges or fantasies. Either type of behavior may be limited to fantasies (sometimes while one is engaged in outwardly non-deviant sex) or acted out with a consenting partner, a non-consenting partner, or in the case of masochism, alone. Sadomasochism occurs in both males and females, and in both heterosexual and homosexual relationships.

### Transvestic Fetishism

This disorder is characterized by heterosexual males who dress in women's clothing to achieve a sexual response. The activity may begin in adolescence, and in secret; later, as an adult, the man may dress as a woman completely and in public. Not all men who cross-dress are unhappy with their gender, but some are. In a small minority of men with transvestic fetishism, gender dysphoria (unhappiness with original gender) may emerge, and those men may eventually seek hormonal treatments or surgical sex reassignment to enable them to live permanently as women.

### Voyeurism

Voyeurism is a paraphilia in which a person finds sexual excitement in watching unsuspecting people who are nude, undressing, or having sex. Voyeurs are almost always male and the victims are usually strangers. A voyeur may fantasize about having sex with the victim but almost never actually pursues this. The voyeur may return to watch the same stranger repeatedly, but there is rarely any physical contact.

Voyeurs are popularly known as "Peeping Toms," based on the 11th century legend of Lady Godiva. According to the story, Tom was a tailor who "peeped" at Lady Godiva as she rode naked through the streets of Coventry, England, in a sacrificial act to get her husband to lower taxes.

### Uncommon Paraphilias

**Bestiality:** Bestiality is a term that describes sexual feelings or behaviors involving animals. Termed zoophilia by DSM-IV this is an uncommon disorder. The disorder does not specify an animal or category of animals; the person with zoophilia may focus sexual feelings on domesticated animals, such as dogs, or farm animals, such as sheep or goats.

**Necrophilia:** Necrophilia is a term that describes sexual feelings or behaviors involving corpses.

**Special Note:** Homosexuality (gay and lesbianism) was previously listed as a paraphilia in the DSM-I and DSM-II, but this was declassified from both DSM-III and DSM-IV,<sup>8</sup> consistent with the change of attitude among psychiatrists and psychologists. Homosexuality is no longer considered a paraphilia.

### GENDER IDENTITY DISORDER

Diagnostic criteria of gender identity disorder as enumerated in DSM-IV include a stated desire to be the other sex, a desire to live and be treated as the other sex, or the conviction that he or she has the typical feelings and reactions of the other sex. In adults, the disturbance is manifested by symptoms such as the preoccupation of getting rid of primary and secondary sexual characteristics and the request for hormones, surgery or procedures to alter physically the sexual characteristics to simulate the other sex. This condition of trans-sexual identity should be persisting for at least 2 years and not be a symptom of other psychiatric disorder and not associated with chromosomal abnormality or a physically intersexed condition. Gender identity disorder, thought to be rare earlier,<sup>60</sup> is being increasingly recognized and many thousand cases have been reported. Many trans-gender individuals may themselves present to the medical practitioner with a request for treatment.

During the past 30 years, the recognition of trans-sexualism or gender identity disorder as a treatable condition requiring psychiatric, endocrine, and surgical intervention has been accepted. Harry Benjamin International Gender Dysphoria Association, the professional body dedicated to the study and treatment of trans-sexualism, has set guidelines known as the "standards of care" which includes, in addition to ongoing psychiatric or psychological monitoring, possible endocrine therapy and depending on the outcome of the graduated trial period of cross-gender living, and possible sex reassignment surgical procedures. The philosophy of treatment is to do reversible procedures before the irreversible ones. Thus clothing change, name change, and cross-gender role socialization would precede endocrine treatment with its gradual somatic changes, followed in carefully selected cases, by surgical treatment.

### Sexual Behaviour in Modern Times

In women with Victorian values sexual responsiveness from them was hardly expected (heightened response even disapproved of) and the effort was to achieve orgasm as soon as possible after



commencement of sexual act. In modern times with the increased expectations of women to have rave or wild sex the stress on the man as performer has increased leading to performance-related anxiety and its consequences. Still more problems have come up with the society opening up on sexual issues, women empowerment, availability of sex toys and sexual pleasure enhancing drugs and gadgets which may take the satisfaction levels to new heights and raise the expectations from the next/new partner. Eventually, the search for the sexual performance boosters continues.

## APHRODISIACS

Aphrodisiacs were agents believed to increase sexual desire<sup>61</sup> and derived its name from Aphrodite, the Greek goddess of love, beauty, and sexual rapture.

The search for such substances dates back millennia. Variety of food, drinks, and animal and vegetal derivatives has been used for this purpose by folk medicines of different cultures. Many substances are used for this purpose: alcohol,<sup>62</sup> opiates (morphine and heroin),<sup>63</sup> cocaine,<sup>64</sup> marijuana,<sup>65</sup> alkyl nitrates.

## Alkyl Nitrites

“Poppers” is a colloquial term for various alkyl nitrites inhaled for recreational purposes, particularly amyl nitrite, butyl nitrite, isopropyl nitrite, and isobutyl nitrite. Amyl nitrite is used medically as an antidote to cyanide poisoning<sup>66</sup> but the term “poppers” refers specifically to its recreational use. These products have also been part of the club culture from the 1970s disco scene to the 1980s and 1990s rave scene. Poppers have a long history of abuse due to the rush of warm sensations and dizziness experienced when the vapors are inhaled. Most often, poppers are used recreationally by men who have sex with men as a sexual enhancer<sup>67</sup> or by substance abusers.<sup>68</sup> Inhaling nitrites relaxes smooth muscles throughout the body, including the sphincter muscles of the anus and the vagina.<sup>66</sup> It is unclear if there is a direct effect on the brain.<sup>69</sup> Smooth muscle surrounds the body’s blood vessels and when relaxed causes these vessels to dilate resulting in an immediate increase in heart rate and blood flow throughout the body, producing a sensation of heat and excitement that usually lasts for a couple of minutes. Alkyl nitrites are often used as a club drug or to enhance a sexual experience (70). The head rush, euphoria, and other sensations that result from the increased heart rate are often felt to increase sexual arousal and desire.<sup>70</sup> It is widely reported that poppers can enhance and prolong orgasms. While anecdotal evidence reveals that both men and women can find the experience of using poppers pleasurable, this experience is not universal;<sup>71</sup> some men report that poppers can cause short-term erectile problems.

## PDE5 INHIBITORS

Sildenafil citrate, a member of the phosphodiesterase type 5 inhibitor family of drugs, is perhaps the latest drug to be used in the search for sexual stimulation. Released by Pfizer with

commercial name Viagra in 1998, sildenafil citrate is the first drug for male erectile dysfunction to be approved by the U.S. Food and Drug Administration. Researchers noticed that the drug seemed to have pronounced success in causing erections.<sup>72,73</sup> Within 2 months after its release there were more than one million prescriptions for Viagra. Despite its billing as an anti-impotence drug, many women are also interested in Viagra to learn if the drug will boost their libidos. PDE5 Inhibitors viz. Sildenafil,<sup>74</sup> Tadalafil,<sup>74</sup> and Vardenafil<sup>75</sup> work by inhibiting the breakdown of GMP-specific phosphodiesterase. This in turn enhances the availability of nitric oxide, which figures in a chain reaction that leads to relaxation in the penis’s smooth muscle, causing an erection.

## DATE RAPE DRUG

The term “date rape drug” refers to a drug that can be used to assist in the commission of a sexual assault or rape. Drugs used may have sedative, hypnotic, dissociative, and/or amnesiac effects, and can be added to a food or drink without the victim’s knowledge. The reasons for drink spiking range from personal amusement or maliciousness to theft or (sexual) assault.<sup>76</sup> The three most commonly used drugs for date rape are alcohol and two other hypnotics viz., GHB, (gamma-hydroxybutyric acid), and benzodiazepines (such as flunitrazepam, also known as *Rohypnol* or “roofies”)<sup>77</sup>; however, an American study showed that alcohol still remains the drug most frequently implicated in substance-assisted sexual assault.<sup>78,79</sup>

## SEX TOYS

Sex Toys are the objects or devices that are primarily used to facilitate human sexual pleasure. The most popular sex toys are designed to resemble human genitals and may be vibrating or non-vibrating. However, the form is not applied to items used for birth control, pornography, or to condoms.<sup>80,81</sup>

A large range of sex toys are available in the commercial market to suit the needs of everyone:

1. Vibrators are vibrating devices intended to pleasurablely stimulate various parts of the body. For sexual use they are often dildo-shaped, although they also come in a wide range of other shapes and sizes.
2. “Artificial vaginas,” also known as “pocket pussies” or “masturbators,” are modeled to accept a penis for simulated intercourse. They can be shaped like vaginas, anuses, or anything with a hole for penetration.
3. A nipple clamp is a clamp used to stimulate the nipples by applying varying degrees of pressure.
4. Butt Plugs are often shorter dildos intended for anal insertion. They tend to have a flared base to prevent the device from becoming lodged in the rectum.

**Sex doll** (also called **love doll** or **blow up doll**)<sup>80,82</sup> is a type of sex toy in the size and shape of a sexual partner for aid in masturbation. The sex doll may consist of an entire body with

face, or just a pelvic part, with the accessories (vagina, anus, mouth, penis) for sexual stimulation. The parts are sometimes vibrating and may be removable or interchangeable.

## Conclusion

Thus it is apparent that the variety of forms of expression of human eroticism is great. They defy schemes of classification. Defining what is sexually normal is highly problematic in any operational sense. The consequential differences between those who seek treatment and those who do not complicates the issue more in clinical practice.<sup>65</sup> In summary management of people with sexual problems is so enmeshed with sociocultural, moral, ethical, legal, and political considerations as to require the clinician to draw upon a diversity of perspectives and skills in order to be effective and to achieve a degree of professional competence in working with these people.

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# Homosexuality, Bisexuality, and Sexual Orientation

David Bradford

99

## Introduction

*"I don't think homosexuality is exactly normal"*—The *British Medical Journal* in 1994 published the results of a study of 28 doctors (20 gay and 8 non-gay) examining homophobia in the medical profession.<sup>1</sup> One non-gay doctor professed not to be prejudiced against homosexuals, but admitted, "Curiously while I am saying this, I don't think homosexuality is exactly normal."

It is over 35 years since the American Psychiatric Association removed homosexuality from its list of psychiatric disorders, but many doctors and health professionals around the world still share the ambivalent feelings of the doctor quoted above. Venereologists and specialists in sexual health medicine are not immune from these feelings despite their experience in dealing with patients exhibiting a wide spectrum of human sexual desire and behavior. Such doctors are not profoundly homophobic; they just find homosexuality and related diverse sexualities (bisexuality, transvestism, and transsexualism) difficult to understand and mildly to moderately uncomfortable to deal with. However, their ambivalent and uncomfortable feelings come across to their differently sexed patients in a thousand subtle ways—in body language, in nuances of verbal expression, and in the way they conduct their clinical management of such patients. Their approach reinforces the attitudes of general society that these people are different, these people are "other," these people are "not exactly normal." And in so doing, health practitioners render their patients a major disservice and potentially harm the public health. This chapter aims to show that ambivalent, uncomfortable or frankly negative feelings on the part of health practitioners to their homosexual or bisexual patients are irrational and harmful, and to point the way towards better medical management.

Homosexual and bisexual men and women are ordinary everyday members of the human race. They are not predatory and they are no more likely to be sex offenders or to engage in pedophilic behavior than their heterosexual peers. In fact, almost all sex offences against children are committed by men and most of these are against female children.<sup>2</sup> Homosexual and bisexual men and women have never threatened the social order and its

institutions, have never been a danger to the prevailing culture and have no inherent bias against religious customs; on the contrary, it has been individual societies which traditionally have criminalized homosexual behaviors and stigmatized individuals of diverse sexuality. A multiplicity of cultures has decreed homosexual activity as aberrant. And most major religions have implacably opposed homosexual practices and expelled homosexual and bisexual men and women from congregations of the faithful (as well as, in most cases, consigning them to eternal damnation). The vehemence and malignity of antihomosexual feeling in so many cultures and countries across the world is difficult to explain on any rational basis and has led (and continues to lead) to much needless and undeserved suffering. It is incumbent on healthcare practitioners to do all they can to alleviate this suffering and to take a stand against homophobic attitudes and practices in society.

## Definitions

The terms homosexuality, bisexuality, sexual orientation, and sexual identity are bedevilled by confusion. The definitions given below may explain the difficulties.

### HOMOSEXUALITY AND HOMOSEXUAL ORIENTATION

To describe a person as "homosexual" can have three rather subtly different meanings:

1. "Homosexual" can describe a person's sexual *behavior*—i.e., a person who predominantly or exclusively has sex with a person or persons of the same sex can be said to be homosexual in *behavior*. Many people whose behavior falls into this category do *not* regard themselves as being homosexual; however, the rather clumsy terms "men who have sex with men" (MSM) or "women who have sex with women" (WSW) have been conjured up to allow meaningful discussion of such activity. Behavioral research occasioned by the human immunodeficiency virus (HIV) pandemic was largely responsible for the development and widespread use of the term "MSM."

2. “Homosexual” can describe a person’s sexual *preference*—i.e., a person whose sexual desire is predominantly directed towards members of the same sex can be said to be homosexual in *orientation*. Because we cannot see into a person’s mind, and because desire or preference might not translate into overt activity, we do not know what an individual’s sexual preference might be unless she or he agrees to divulge that information about themselves. It is probable that a significant proportion of the population prefer to keep their true sexual desires and yearnings secret.
3. “Homosexual” can describe a person’s sexual *identity*—i.e., a person who adopts a sexual life style which is consistent with and self-defined by same sex desire and same sex behavior can be said to have a homosexual identity. Males who adopt a homosexual identity are often referred to as gay while females who adopt a homosexual identity are referred to as lesbian.

## BISEXUALITY

Bisexuality is even less clearly defined than homosexuality, but the term can have three rather different meanings:

1. “Bisexual” can describe a person’s sexual *behavior*. It is obviously a term that can be applied to a person who has sex with both males and females. In this strict sense, a significant number of people who would prefer to describe themselves (or identify) as either “homosexual” or “heterosexual” might demonstrate bisexual behavior intermittently or even on a regular basis.
2. “Bisexual” can describe a person’s sexual *preference* or desire—i.e., a person whose sexual desire is directed towards members of both sexes can be said to be bisexual in *orientation*. The same caveat that applies to meaning number 2 for “homosexuality” equally applies here.
3. “Bisexual” can describe a person’s sexual *identity*—i.e., a person who adopts a sexual life style, which is consistent with and self-defined by sexual desire for persons of both sexes and sexual behavior with members of both sexes can be said to have a bisexual identity.

Meaning number 3—sexual *identity*—is very much a western social construct and may have little relevance or meaning outside industrialized western countries. Large parts of the adult population of the world get by very nicely without having to define themselves as “gay” (a homosexual man), “straight” (a heterosexual man or woman), “bisexual” (man or woman who is sexually versatile) or “lesbian” (a homosexual woman). They regard themselves merely as men or women and do not seek to create a specific identity based on their predominant (or occasional) sexual activities or desires. Although nature itself never stoops so low, western culture disliking disorder and messiness feels the need to “tidy people up”—especially minorities, and get them into correct boxes with the right labels attached.

## OTHER NON-WESTERN SEXUAL IDENTITIES

In parts of the world other than the industrialized west, some minority groups of biological males adopt other gender roles from time-to-time or continuously. These groups may be visible as men who act in an exaggeratedly effeminate manner or who dress and behave as women. Such men may participate in sexual activity with other men and may indeed attract male sexual partners from other groups of males in the community who act in an exaggeratedly masculine manner but yet predominantly choose to have sex (where they assume the “male” insertive role) with men from cross dressing or effeminate groups. These groups defy conventional categorization but can all be described as men who have sex with men (MSM).

In the Indian subcontinent, the most prominent groups are:

- *Hijras*—transgendered MSM, sometimes regarded as a “third sex.” They are often castrated, dress as women and are part of a clearly identified social group, which is tolerated by society but sometimes feared as well.
- *Kothis* (also called *Metis* in Nepal)—these are MSM who adopt an effeminate lifestyle but who nevertheless may be married and father children.
- *Panthis* (also called *Ta* in Nepal)—these are masculine men who although passing as ordinary males in the community sometimes have insertive sex with *Kothis*. They do not self identify but are labeled or nick-named *Panthis* by the *Kothis*.

In Southeast Asia, there are many groups of MSM, but some of the more prominent and better known ones include:

- *Katoey* (Thailand and Laos), *Kteuy* (Cambodia), and *Waria* (Indonesia)—these are transgendered MSM, sometimes cross-dressing and sometimes engaging in sex work where they attract a sub-group of masculine males who prefer sex with transgendered men.
- *Sray sros* (Cambodia)—these are men who identify as women and who dress as women to attract male sexual partners. They are also known as “long hairs” in English.
- *Pros saat* (Cambodia)—these are masculine acting MSM (also called “short hairs” in English) who may choose to have sex, where they adopt the masculine insertive role, with *Sray sros*.<sup>3</sup>

## Etiology

Theories abound about the origin of homosexuality. Factual knowledge is far more elusive. Given the enormous diversity of sexual desire and behavior in human beings around the world it is not surprising that so little is known about causative factors. Any successful theory about the origin of homosexual desire must account for the curious fact that homosexuality and bisexuality are such persistent human traits. By the very nature of exclusive same-sex sexual activity there would seem to be no evolutionary advantage—rather the reverse. Why did homosexual tendencies not die out centuries ago? We have seen already that human societies and cultures, with very few exceptions, have been

implacably opposed to the expression of a homosexual lifestyle, yet people with same sex desires have persistently and inexplicably done what comes naturally to them in every country, under widely varying cultures and throughout all epochs of time, often to their considerable individual disadvantage. The sex drive is deep and strong and the libido will have its way whatever the consequences! Carl Westphal (1833–1890), the Berlin psychiatrist with the dubious honor of being the first medico to label homosexuality a disease, at least recognized the existence of an “instinctive urge stronger than the will, driving some individuals to find sexual pleasure with others of the same sex.”<sup>4</sup> Despite the inherent fascination in the topic, for the limited purposes of this Chapter we can get little further than the not so profound summing up in a 2006 article: “Finally I argue that exclusive same sex attraction in human males is due to an interaction between genetic, cultural, developmental, and psychological factors.”<sup>5</sup>

## Prevalence of Homosexuality and Bisexuality

The prevalence of homosexuality and bisexuality depends upon the definition the researcher is adopting. Clinicians who work in sexual health are more interested in homosexual and bisexual *behavior* than they are in sexual identity or preference because it is behavior which places people at risk for sexually transmissible agents, including HIV. Social biologists, psychologists, and anthropologists on the other hand will be interested in sexual preference and identity as well as behavior.

In several western countries, large population surveys of adult sexual behavior have been carried out in the past decade or two. These have revealed that the percentage of males and females who identify as gay, bisexual or lesbian is small. The Australian Study of health and relationships found that only 1.6% and 0.9% of men *identified* as homosexual or bisexual respectively, while 0.8% and 1.4% of women *identified* as homosexual or bisexual.<sup>6</sup> These figures accord well with similar studies done in other western countries.<sup>7</sup>

However higher percentages of people, including people who identify themselves as heterosexual, report same-sex *desire* or attraction. The Australian study reported 8.6% of men had experienced some same-sex attraction or some sexual experience with another male, while 15.1% of women had felt sexually attracted to other women or had some sexual experience with the same sex.<sup>6</sup>

In other parts of the world, and particularly in Asia and Southeast Asia, the true prevalence of same-sex sexual behavior is unknown. Homosexuality and bisexuality remain largely invisible within mainstream society because the socially recognized categories in the West such as gay, lesbian or bisexual around which men who have sex with men and women who have sex with women can frame their sexuality do not exist. In these countries MSM and WSW form extremely heterogeneous populations marked by a diversity of sexual self-perception and sexual activity.<sup>8</sup> While there are no published estimates of the prevalence of female same-sex behavior anywhere outside western countries,

population-based studies have suggested that the prevalence of male–male sexual activity in Asia is similar to or higher than that established for the West, and that large numbers of MSM also have sex with women. AmfAR’s 2006 Report ‘Treat Asia’ comments wryly “Asia has more than enough male–male sex to fuel an (HIV) epidemic.”<sup>3</sup>

## Homosexuality and Clinical Practice

For the practising healthcare provider, academic debate about the nature of homosexuality or bisexuality is largely non-productive and unhelpful. Homosexual desire and same-sex sexual activity are simply facts of life, as they have always been. Yet homosexual desire and behavior exert an influence on the health of those affected which can have far reaching effects both for the individual and the public health. A young person who reaches the turmoil of puberty and adolescence and discovers that her or his sexual desires are directed towards members of the same sex (as is the case for 8–15% of that population<sup>6</sup>) can find this a troubling and isolating experience. If that young person is fortunate and lives in a family and a culture where homosexuality and bisexuality is recognized as part of the normal wide spectrum of human sexual orientation and behavior, then she or he is likely to weather the storm well. But if, as will be the case for most young people around the world, she or he lives in a family and a culture where homosexual desire and behavior are regarded as abnormal, abhorrent or even evil, the effects on that young person’s mental, physical, and sexual health may be serious and even life-threatening. The link between youth suicide and homosexuality particularly in young men is now well established.<sup>9</sup> Where sexual behavior is stigmatized, the societal pressures brought to bear on those whose sexual desires force them to act beyond the bounds and limits set by prevailing social mores are very strong—strong enough indeed to lead to deep depression and suicidality in vulnerable individuals. For others who reach some adjustment and accommodation with their sexuality, the fact of their sexual difference in a hostile environment means they have to resort either to a life of repression where their true sexual desires and needs are never met, or a double life—a life that on the surface accords with society’s demands but covertly includes stratagems, which allow the individual some sexual relief usually in clandestine and anonymous associations with like-minded men or women. These two main methods of coping—either sexual repression or trying to lead a double life—can place strains on people which can be barely tolerable over time and may result in substance abuse or poor health. There is good evidence that alcohol abuse and nicotine dependence are commoner in homosexual men and women. Cardiovascular disease and mental health problems are also more common than in heterosexual peers.

## Sexual Health and Homosexual or Bisexual People

Women who have sex with women (WSW) and who never have sex with male partners seem relatively free of sexually



transmitted infections (STIs). However, infections that do not require penetrative sex for transmission (like human papilloma virus [HPV] and the herpes simplex viruses [HSV1 and HSV2] for example) are theoretically capable of being passed on by woman-to-woman sexual contact and indeed are seen in clinical practice in WSW. The curious condition bacterial vaginosis (BV) is also significantly associated with WSW. HPV infection of the cervix can be acquired through sexual activities between lesbian women so even exclusive WSW should be advised that they still require regular cervical cytology (Pap Smears). Bisexual WSW are obviously at the same risk of STIs as exclusively heterosexual women and the risk depends on whether male partners carry any sexually transmissible micro-organisms.

STIs, including human HIV infection, have always been a significant blight on the lives of men who have sex with men (MSM). There are strong hints from the writings of classical authors of Greece and Rome that this fact was recognized even then. In 2008, UNAIDS reported that HIV infections among MSM were increasing sharply in parts of Asia and that only 40.1% of MSM in 27 reporting countries were reached by HIV prevention programs between 2005 and 2007.<sup>10</sup> A grave crisis now exists in the explosion of HIV infection rates among MSM throughout the whole of the Asian continent.

This fact is not surprising; Table 99.1 lists the biological and sociological reasons why STIs are common in MSM, especially in homophobic societies.

We clinicians cannot escape censure. Unfortunately, there are also strong medical reasons why STIs and HIV remain uncontrolled in MSM (see Table 99.2). These facts are applicable in all countries and societies and are not just confined to regions where homosexual behavior is illegal and stigmatized. Clinical testing and management of patients giving a history of male–male sexual activity is covered in other chapters in this textbook, but it is vital to stress that the clinician's overall attitude towards MSM patients is important not just for the individual patient's benefit but also for the public health. Because world-wide, a high percentage of MSM also have sex with women, the potential for wider spread of HIV and other STIs through bisexual behavior is great. Good management and early diagnosis and treatment of MSM for STIs will do much to reduce this risk.

## Conclusion

Homosexuality and bisexuality are part of the human condition. The quality of the relationship between countless same-sex couples down through the centuries (some famous and well-known people, most obscure and ordinary folk) attests to the fact that homosexual love can be as strong, deep, and lasting as heterosexual love. Love between adult individuals should always be respected and should never be criminalized. Sex is a vital essential part and expression of love. Society's refusal to accord same-sex love the respect and equality given to heterosexual love has been the direct cause of almost all the problems attributed to homosexual behavior in the past and down to the present time. In this matter,

**Table 99.1:** Reasons for High Prevalence of STIs in Men Who Have Sex With Men

Biological
Men possess a penis
Penises are penetrative organs
Penises are designed to transmit semen (along with anything else in seminal fluid!)
Highly receptive columnar epithelial surfaces are involved in male-to-male sex: <ul style="list-style-type: none"> <li>• Rectal mucosa</li> <li>• Anorectal squamo-columnar junction</li> <li>• Oropharyngeal and tonsillar mucosa</li> <li>• Urethral meatal mucosa</li> <li>• Inner surface of prepuce (foreskin)</li> </ul>
Sociological
Myths and ignorance abound about male-to-male sex—e.g., in countries where HIV transmission is predominantly heterosexual, many men believe sex with men is safer
Barrier protection is not needed to prevent reproduction, so condom use is rare
Illegality discourages open expression of male-to-male love or sexual behavior
Societal stigmatization directly discourages regular open relationship between two males
Societal stigmatization thus indirectly encourages multiple casual partners
Male-to-Male sexual activities are often covert: <ul style="list-style-type: none"> <li>• Fleeting opportunistic contacts</li> <li>• Frequently contacts are anonymous</li> <li>• Frequent concurrent disinhibiting substance use (especially alcohol)</li> <li>• Sex may be in dimly lit places, so partner not clearly seen; protection difficult</li> <li>• Opportunistic male-to-male sex work common in homophobic societies</li> </ul>

**Table 99.2:** Medical Reasons for Poor Control of STIs (& HIV) in MSM

Patient-centred	Clinician-centred
Shame and guilt	Discomfort with homosexuality
Lack of self-esteem	Ambivalent feelings about MSM
Fear of clinician's disapproval	Judgemental or moralistic approach
Fear of consequences of self-disclosure	Irrational fear of contamination from MSM
Decreased health seeking behavior	Not swabbing the correct anatomical sites
Giving an untrue sexual history if symptomatic	Ignorance about testing and management of STIs in MSM

society is clearly behaving irrationally. In the words of Australia's recently retired High Court Judge, Justice Michael Kirby: "this irrationality has to stop, the denial and hatred have to come to an end."<sup>11</sup>

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## Introduction

Clinical and epidemiologic studies exploring sexual attitudes, behaviors, and clinical conditions among women who have sex with women (WSW) are lacking. Existing literature, though sparse, does contain important findings in the field of sexually transmitted infections (STI) among WSW. This chapter highlights sexual health risks and clinical conditions among WSW.

It is worth exploring terminology in the arena of sexual health among WSW. There are three terms that deserve description: sexual orientation, sexual identity, and sexual behavior. Each of these conveys information about an individual's same-sex attraction and behavior and is readily confused with each other. According to the American Psychological Association, sexual orientation describes emotional, romantic, or sexual attraction toward others.<sup>1</sup> This may be different than sexual identity, which is how a person labels oneself in terms of a place within a specific community (lesbian, bisexual, or queer, for example). Sexual behavior describes specific sexual practices despite orientation or identity, and is most relevant when attempting to estimate risks of incident disease in the context of STI.

Terms commonly used in the scientific literature include "WSW" to refer to women whose primary sexual partnerships are with women, and "WSMW" to refer to women who report sex with men and women. However, the time frame over which sexual contact with men is used to differentiate between these two designations can differ considerably among studies, ranging from the past 90 days through a woman's lifetime. Thus, no universal definitions exist for WSW and WSMW.

## Epidemiology

Data collection occurring as part of most large epidemiologic studies has largely omitted specific categorization of WSW. In the US, two landmark women's health surveillance projects, the Women's Health Initiative (WHI) and the Nurse's Health Study, only began collecting information on same-sex behavior or identity in 1998 and 1995, respectively (DHHS, 2000). More recently, population-level data have become available for some industrialized countries.

According to the US National Survey of Family Growth from 2002, 11% of women aged 15–44 reported same-sex behavior in their lifetime. This report was based on a sample of 12,571 men and women and collected information of sexual behavior using audio computer-assisted self-interviewing (A-CASI).<sup>2</sup> In Britain, the National Survey of Sexual Attitudes and Lifestyles (NATSAL) 2000 study collected information on the sexual behavior of 11,161 residents age 16–44.<sup>3</sup> Of the female respondents, 4.9% reported same-sex behavior including genital contact and 2.8% reported some same-sex behavior in the past year. Notably, 98% of WSW reported a history of sex with men at some point in their lifetimes and 85% reported that they have had sex with at least one man in the past 5 years. In a study conducted in 2003 in Australia of 9134 randomly selected women between 16 and 59, 0.8% of them identified as lesbian, 1.4% as bisexual, and 15.1% reported same-sex attraction or sexual experience.<sup>4</sup> No data are available on the prevalence of WSW in resource-limited countries, despite a recent burgeoning of information on report of same-sex behavior among men in sub-Saharan Africa.<sup>5,6</sup>

## Risk Behaviors

According to multiple studies, the majority of WSW (between 80% and 95%) report a sexual history with men, with much of this behavior commencing during adolescence.<sup>7,8</sup> Diamant and colleagues surveyed 6935 self-identified lesbians solicited through a survey printed in *The Advocate*, a US-based national gay and lesbian news magazine. The majority of women in this study (77.3%) reported one or more lifetime male sex partners. Of these women, 17.2% reported having anal intercourse and 5.7% reported a male sex partner in the past year.

Alcohol abuse, illicit drug use, and exchange of sex for drugs or money are known high-risk behaviors that are suggested to be more prevalent among WSW.<sup>9–14</sup> One relatively large cross-sectional survey across healthcare sites in the US found that women who identified as lesbians reported more male sex partners and higher numbers of homosexual male sex partners in the past year than either heterosexual or bisexual women.<sup>15</sup>



**Table 100.1:** Risks and Characteristics by Report of Drug Use in the Past Year

Behavior/Clinical characteristic	Methamphetamine RR (95% CI)	Cocaine RR (95% CI)	MDMA (Ecstasy) RR (95% CI)	Heroin RR (95% CI)	Marijuana RR (95% CI)
Sex with any new male SP, 60 days	3.17 (1.4–7.1)*	3.46 (1.8–6.5)*	2.74 (1.4–5.4)*	3.81 (1.2–11.8)	1.69 (0.8–3.5)
Vaginal intercourse with a male SP, 90 days	2.40 (1.4–4.1)*	2.70 (1.8–4.0)*	2.49 (1.6–3.8)*	1.79 (0.6–5.3)	2.21 (1.3–3.7)*
More than 1 male SP, 90 days	3.61 (1.1–9.1)*	4.64 (2.0–10.6)*	3.87 (1.6–8.8)*	5.45 (0.9–12.5)	6.58 (1.6–40.5)*
Anal sex, male or female SP, 90 days	1.50 (1.1–2.0)*	1.31 (1.1–1.7)*	1.35 (1.0–1.7)	0.77 (0.3–2.3)	1.14 (0.9–1.5)
Self-reported history of <i>C. trachomatis</i> infection	4.56 (1.7–12.2)*	2.95 (1.2–7.1)*	3.01 (1.2–7.6)*	3.18 (0.5–19.4)	2.32 (0.8–6.9)
Reporting ever having traded sex for money or drugs	4.25 (1.5–9.5)*	3.43 (1.5–7.6)*	1.2 (0.3–3.3)	10.8 (3.7–14.0)*	1.00 (0.4–2.3)

\* $P < 0.05$  Abbreviations: RR, relative risk; SP, sex partner.

This study included 1304 lesbians across 33 outpatient primary care sites who completed an extensive questionnaire (98 items) with a good response rate (>50%). Respondents were mostly white, highly educated, and had a relatively high income. Although most women reported being in a stable relationship (71%), many (23%) reported substance use while having sex or sex with a homosexual or bisexual man (6%) in the past year. Of those women who recently had sex with men ( $N=600$ ), only a little over half reported ever using condoms. Table 100.1 details findings from one analysis in Seattle, Washington, US, on use of illicit drugs among 336 WSW and WSMW aged 16–35 years. Use of MDMA (ecstasy), methamphetamine, and cocaine were all associated with sex with new male partners, multiple male partners and self-reported history of *Chlamydia trachomatis* (*C. trachomatis*) infection. Also, use of methamphetamine and cocaine were associated with increased risk of recent anal sex.<sup>16</sup>

Consistent with sexual histories with men, lifetime prevalence of reported pregnancy ranges from 23% to 35% among WSW.<sup>17,18</sup> Among 392 WSW who participated in the Seattle Lesbian Health Study (1998–2001; median age of all subjects, 28 years), 25% reported a prior pregnancy, over half had used oral contraceptives, and 16% had had an induced abortion.<sup>19</sup>

Specific higher risk sexual behaviors among WSW in Britain were reported in the NATSAL 2000 study.<sup>3</sup> Interestingly, WSW who reported male partners, as compared with heterosexual women, more commonly reported anal sex (age-adjusted odds ratio for WSW relative to women reporting exclusively heterosexual partners [AOR] 2.46 [95% CI 1.58–3.85,  $P < 0.001$ ]). Similarly, WSW, when compared with heterosexual women, most commonly reported a recent partner described as “not regular” (AOR 1.74 [95% CI 1.07–2.82,  $P = 0.02$ ], initiating sex less than 24 hours after meeting most recent partner (AOR 2.48 [95% CI 1.44–4.27,  $P = 0.001$ ]) and unsafe sex (two or more heterosexual partners in the past 4 weeks with inconsistent condom use; AOR 7.17 [95% CI 3.25–15.8,  $P < 0.001$ ]). Moreover, WSW were more likely than heterosexual women to report seeking care at an STD clinic, obtaining an HIV test, being diagnosed with any STI and having had an induced abortion ( $P < 0.001$  for each relative to heterosexual respondents).

Interestingly, studies that have evaluated same-sex behavior among adolescents in the US have found some disparate findings between WSW and WSMW. In one study of more than 29,000 sexually active female college students, self-identified bisexual women reported a history of more STIs than either their heterosexual or self-identified lesbian counterparts.<sup>20</sup> In one analysis among WSW 14–44 years of age, self-reported viral STI rates were significantly higher among self-identified bisexual women (15.0–17.2%) than among self-identified lesbians (2.3–6.7%).<sup>21</sup> These findings support the need to carefully assess sexual history in terms of prior and current risk behavior for more focused and optimal screening and education.

## Sexual Behaviors and Sexually Transmitted Infections

Table 100.2 provides an overview of sexual behaviors commonly practiced by WSW. The consensus from the available data is that over 95% of WSW engage in oral-vulvar/vaginal sex (cunnilingus) or oral-anal sex (anilingus). These activities provide the opportunity for transmission of a variety of pathogens. There was an outbreak of *Entamoeba histolytica* in Canada among WSW and WSMW engaging in oral-anal sex, providing evidence of the broad possibilities of transmission of enteric pathogens.<sup>22</sup> WSW also commonly practice digital-vaginal sex and digital-anal sex (“fingering” or “fisting”) and frequently also use sex toys inserted vaginally and/or anally. The proportion of women who engage in sadomasochism is unclear, but this behavior obviously may expose women to exchange of blood.

Many of the sexual behaviors practiced by WSW present a plausible means for exchange of infected cervicovaginal secretions and blood if barriers are not used. This possibility is supported by reports of transmission of genital human papillomavirus (HPV), genital herpes, *C. trachomatis*, syphilis, trichomoniasis, and HIV among this group.<sup>23–28</sup> Despite these reports and studies over the past two decades that describe STI among WSW, many women and healthcare providers remain under the false assumption that WSW are at no risk.

Other sexual behaviors that WSW commonly practise include mutual masturbation, kissing, and massage. Additionally,

**Table 100.2:** Sexual Practices among Women who have Sex with Women<sup>10,22,59,72</sup>

Practice	Vernacular name	Estimated frequency <sup>10,22,59,72</sup>	Factors modifying risk of STD <sup>†</sup>
Oral-vulvar/vaginal contact (cunnilingus)	Going down Active = Top Receptive = Bottom	Very common (>95%)	<ul style="list-style-type: none"> <li>• Presence of oral lesions in active partner (herpes, syphilis, possibly gonorrhea) (+)</li> <li>• Use of barriers (plastic wrap, dental dams, condoms)</li> </ul>
Digital/vaginal-contact (digital-anal contact)	Fingering Fisting (top or bottom)	Very common (95%)	<ul style="list-style-type: none"> <li>• Sharing of infected cervicovaginal secretions (trichomoniasis, <i>C. trachomatis</i>, gonorrhea, HPV, herpes) (+)</li> <li>• Use of gloves (–)</li> </ul>
Oral/anal contact	Anilingus Rimming	Common (35%)	<ul style="list-style-type: none"> <li>• Presence of oral infection in performing partner (syphilis, genital herpes) (+)</li> <li>• Presence of anorectal infection in receiving partner (Hepatitis A, <i>E. histolytica</i> and other enteric pathogens) (+)</li> <li>• Use of barriers (–)</li> </ul>
Insertive sex toys (to vagina or anus)	Toys, dildos	Common vaginally (60%) and anally (25%)	<ul style="list-style-type: none"> <li>• Sharing of infected cervicovaginal or anal fluid (trichomoniasis, <i>C. trachomatis</i>, gonorrhea, HPV, herpes) (+)</li> <li>• Use of condoms with sex toys (–)</li> <li>• Sharing insertive toys without cleansing prior to use (+)</li> </ul>
Direct genital-genital contact	Tribadism	Very common (95%)	<ul style="list-style-type: none"> <li>• Direct contact of susceptible skin/mucosa (HPV, herpes, syphilis) (+)</li> <li>• May involve use of interposed devices, such as vibrators, which can cause mechanical vulvar irritation</li> </ul>
Sadomasochism	S & M, Bondage	Unknown	<ul style="list-style-type: none"> <li>• Sharing of blood (hepatitis B, C, HIV) (+)</li> </ul>

\*Refs. 10, 22, 59, and 72.

†Plus sign (+) denotes factor likely to enhance risk of STI transmission or acquisition; minus sign (–) denotes factor with probable protective effect

tribadism or frottage, which is defined as genital rubbing by any part of the other woman's body, often the thighs, legs or trunk, is also commonly practiced but thought to be relatively low risk for transmission of STI. There is, however, theoretical risk of HSV and mite transmission with close mucosal or skin-to-skin contact. (McNair, Sexual Health, 2005) Table 100.3 compares the rates of self-reported or clinically diagnosed STIs in a range of studies. Further discussion on each of these STIs and on bacterial vaginosis (BV) follows.

## GENITAL HUMAN PAPILLOMAVIRUS

Certain strains of HPV cause genital warts, the majority of cervical cancer, and some types of anal cancer. HPV has been detected in WSW, including those with no prior history of sex with men. Two research efforts based in the US (Seattle Lesbian Health Study) enrolled WSW to assess HPV DNA by PCR-based methods in cervical, vaginal, and vulvar samples.<sup>25,27</sup> Among 150 women in the earlier of these two studies (1995–1997), HPV DNA was present in 30% of all subjects and in 19% of those who reported no lifetime history of sex with men. Among all subjects with detectable HPV DNA, 29 (69%) had unclassified types only, 9 (21%) had HPV-31/33/35/39, 8 (19%) had HPV-16, and 1 (2%) had HPV-6/11. Twenty-eight (62%) had HPV DNA detected in the specimens from the cervix, 26 (58%) from the vagina, and 32 (71%) from the vulva. Among the 41 women with HPV DNA who did report prior sex with men, 21 (51%) had not had sex with a male partner in over a year (range, 1–18 years; median, 2 years). Women with detectable HPV DNA who reported male sex partners were more likely to report a history of receptive oral sex ( $P=0.05$ ).

In a follow-up to the initial work on HPV among WSW, researchers in the Seattle Lesbian Health Study enrolled women between 1998 and 2001 and measured HPV DNA in 248 women, detecting it in 31 (13%), including 7 with HPV type 16 and 15 with other oncogenic types. Twelve (39%) had non-oncogenic types (6/11, 40/42/53/54). Among the 28 women with HPV DNA who reported prior sex with men, 14 (50%) had not had sex with a male partner in over a year (range, 1–11 years; median, 2 years). Importantly, both high- and low-grade squamous intraepithelial lesions (SIL) were detected on Pap smear testing in both of these studies, including among women with no history of sex with men. In the first study, 13 (6% of all subjects) of 150 participants had abnormal Pap smears with 3 of these women reporting no prior sex with men and 3 women reporting female partners with genital warts. Among 248 women enrolled in the second study, 7 of 11 SIL detected occurred in women who reported no prior sex with men or sex with men more than 1 year previously. Twenty-five women (10% of all subjects) had abnormal Pap smears. Four women had high-grade and 7 had low-grade SIL with 7 of these lesions occurring in women who reported no history of sex with men or sex with men more than one year prior to testing. HPV DNA was detected in 7 of the 11 women with SIL (HPV-16 in 3 women and other oncogenic types in 4 women). Discussion of Pap smear testing as cervical cancer screening among WSW follows in the section of this chapter on Preventive Health.

## GENITAL HERPES

Both herpes simplex virus (HSV) type-1 and HSV type-2 occur among WSW, with some suggestion that HSV-1 is more

**Table 100.3:** STI Rates for Women who have Sex with Women Compared with Australian National Data

Studies	Diamant et al., <sup>11</sup> 2000	Bailey et al., <sup>39</sup> 2004		Fethers et al., <sup>10</sup> 2000		Grulich et al., <sup>73</sup> 2003
Country of study	USA National	UK London		Australia Sydney		Australia National
Data source	LGBT magazine	Two lesbian sexual health clinics		STI clinic		Population based
Method	Self-report survey	Self-report survey		Case notes Matched het		Self-report phone survey
Number	6935	708		1408 + 1423 controls		9 578
Sexuality identity	100% WSW	97% WSW 1% WSMW		100% ever reported sex with women (het controls)		0.8% WSW 1.4% WSMW 97.8% het
Female partners only-lifetime	22.4%	17.9%		7.0%		NA
Lifetime diagnosis for women with female partners only	6%	—		—		NA
Lifetime diagnosis of any STI	17%	WSMW 56%	WSW 49%	WSW 44% <sup>†</sup>	Het 32%	16.9% <sup>‡</sup> • 16.6% het • 23.4% WSW • 37.9% WSMW
STI clinic diagnosis %	—	—	—	—	—	—
Candida	NA	18.8	10.5	13	16	57.6
Bacterial vaginosis	NA	31.5	30.7	8 <sup>†</sup>	6	1.8
Trichomonas	6	1.4	0.8	NA	NA	0.8
Genital warts	4.8	1.7	0.8	8 <sup>†</sup>	11	4.4
Chlamydia	4.6	0.7	0	3	4	3.1
Genital herpes	3.3	1.2	0.8	9	9	2.5
Gonorrhea	1.6	0.3	0	<1	<1	0.6
PID	2.0	NA	NA	NA	NA	2.3
Hepatitis B	NA	NA	NA	5 <sup>†</sup>	3	0.7
Hepatitis C	NA	NA	NA	5 <sup>†</sup>	<1	0.5
HIV	0.1	NA	NA	<1	<1	NA
Syphilis	0.3	NA	NA	NR	NR	0.1

<sup>†</sup>Significant difference, NA = not asked; het = heterosexual.

<sup>‡</sup>The STI self-reported rates for this study are reported for the whole study population.

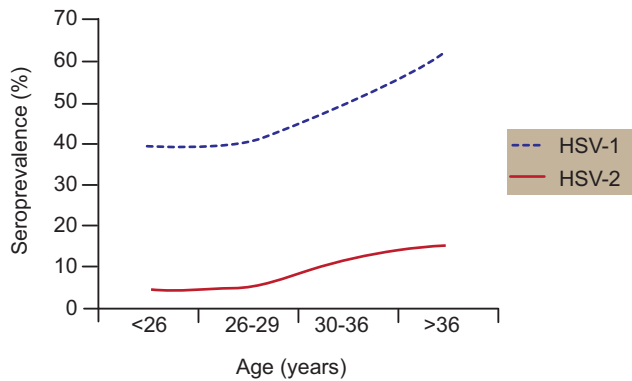
prevalent in this population. Genital herpes is classically caused by HSV-2 but can also be secondary to HSV-1. Among the 392 women enrolled in the Seattle Lesbian Health Study, antibodies to HSV-1 were detected in 46% and antibodies to HSV-2 in 8% as determined by Western blot assay.<sup>26</sup> Moreover, HSV-1 seroprevalence increased significantly with increasing numbers of female partners, suggesting that oral-genital transmission of this virus might be relatively common. Of 78 women who reported no prior sex with men, 3% were HSV-2 seropositive.

Findings from the Seattle study are slightly disparate from those of the US National Health and Nutrition Examination Survey (NHANES) study that tested sera collected between the years 1999 and 2004 on a population presumed to be predominantly heterosexual.<sup>29,30</sup> The seroprevalence of HSV-2 among women age 20–29 years old was 15.6%, roughly double that of the seroprevalence from the Seattle study. This could be explained, in part, by less efficient genital transmission of HSV-2 in the absence

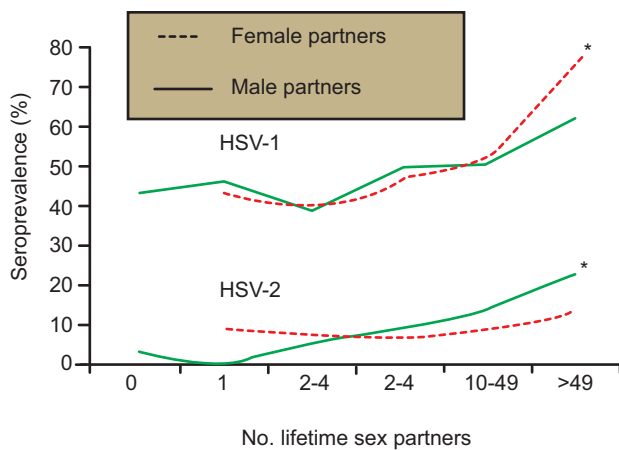
of penile–vaginal sex. Additionally, the Seattle based study largely comprised white women who reported long-term monogamous partnerships. Predictors of HSV-2 infection in the NHANES study included race, age, lifetime number of sex partners (gender not specified), and marital status. Other predictors included fewer years of formal education, income below the poverty level, and history of cocaine use. Of these, increasing age was the only independent predictor for HSV-2 seroprevalence in the Seattle Lesbian Health Study (see Fig. 100.1).

Because genital infection with HSV-1 is most likely acquired during receipt of oral sex, a behavior probably practiced more frequently by WSW than heterosexual women, WSW may be at increased risk. Some studies support that the incidence of genital infection with HSV-1 is increasing and that new genital HSV-1 infections are as common as oropharyngeal HSV-1 infections.<sup>31–34</sup> Receptive oral sex in the absence of vaginal intercourse among 1207 heterosexual women prospectively followed in Pittsburgh increased





**Fig. 100.1:** Seroprevalence of HSV by Number of Lifetime Sex Partners. (With permission from Marrazzo JM, Stine K, Wald A. Prevalence and risk factors for infection with herpes simplex virus type-1 and -2 among lesbians. *Sex Transm Dis* 2003;30:890–5.)



**Fig. 100.2:** Sexual Behaviors of Women who have Sex with Women. (With permission from Marrazzo JM, Stine K, Wald A. Prevalence and risk factors for infection with herpes simplex virus type-1 and -2 among lesbians. *Sex Transm Dis* 2003;30:890–5.)

the risk of HSV-1 seroconversion (9.8 versus 1.2 cases per 100 woman-years of follow-up;  $P=0.04$ ).<sup>35</sup> Data from the Seattle study supported a stronger association between number of lifetime female sex partners and HSV-1 infection (Fig. 100.2) than among those who reported male sex partners in the NHANES study.<sup>30</sup>

### CHLAMYDIA TRACHOMATIS AND NEISSERIA GONORRHOEA

*C. trachomatis* is the most common bacterial STI in the world with a global burden of almost 92 million cases based on a World Health Organization (WHO) estimate from 1999 and an estimated 4–5 million cases in the US alone reported annually to the Centers for Disease Control and Prevention (CDC) in 2009.<sup>36</sup> *C. trachomatis* has a major impact on women's sexual and reproductive health. Untreated infections can lead to pelvic inflammatory disease (PID), tubal infertility, and chronic

pelvic pain. Because the majority of infections in women are asymptomatic and do not cause visible signs of cervicitis, the CDC and the United States Preventive Services Task Force recommend annual screening for all women aged 24 years and younger.<sup>37,38</sup> Despite the widespread prevalence of *C. trachomatis*, little data at the clinic, community or population level is available that describe its prevalence among WSW.

There are no reliable reports of documented transmission of either *C. trachomatis* or *N. gonorrhoeae* among WSW. For example, among 709 new patients attending a clinic for lesbians in London, prevalence of *C. trachomatis* was 0.6% and gonorrhea was 0.3%.<sup>39</sup> Another study based in an STD clinic in Seattle, Washington revealed *C. trachomatis* among only 2 (1.1%) of 187 women reporting sex only with women in the past 2 months and in 12 (1.9%) of 841 women reporting sex with both men and women during that time frame. *N. gonorrhoeae* was detected in 0 of 192 women and 14 (2.1%) of 661, respectively.<sup>18</sup>

More recently, in an analysis of 9358 visits with tests for *C. trachomatis* among WSW and WSMW attending family planning in the US Pacific Northwest from 1997 to 2005, *C. trachomatis* positivity, a proxy for clinic-based prevalence, was 7.1% among both WSW and WSMW compared with 5.3% among heterosexual women tested during the same time frame. Behavioral risks were more commonly reported by women reporting same-sex behavior compared to heterosexual women. WSW with *C. trachomatis* infection were more likely to have clinical findings (including cervical ectopy, friable cervix, PID or cervicitis) (OR 3.5 [95% CI 2.3–5.3],  $P<0.05$ ) compared to WSM (OR 3.1 [95% CI 3.0–3.3],  $P<0.05$ ) and WSMW (OR 2.5 [95% CI 1.7–3.8],  $P<0.05$ ). Risks for *C. trachomatis* positivity were comparable across the groups and included younger age, non-white race, behavioral risks, and clinical signs of infection.<sup>40</sup> The authors concluded that until more data are available to clarify the epidemiology and risks associated with this common infection, WSW should undergo routine age-based screening for *C. trachomatis* as recommended for heterosexual women. It is theoretically plausible that exchange of cervicovaginal secretions between women may provide the opportunity for *C. trachomatis* transmission in this group.

### HUMAN IMMUNODEFICIENCY VIRUS AND SYPHILIS

As discussed in the prior section on sexual risks behaviors, some data suggest that some WSW engage in higher risk sexual behaviors, including sex with men who have sex with men (MSM), relative to their heterosexual counterparts. Given this, some WSW may be at risk for STI prevalent in MSM. Risk of HIV transmission varies with sexual behaviors, including exchange of cervicovaginal secretions, or exchange of blood in the setting of vulvar or vaginal abrasions, during menses or as a consequence of sexual activity.

While no large scale studies have been conducted on WSW and HIV, there have been case reports of HIV transmission between women, including women who report sex exclusively with women.<sup>30,41–45</sup> Kwakwa reported a 20-year-old woman who

have had sex exclusively with a bisexual HIV-infected partner for 2 years prior to being diagnosed with a genetically identical strain of HIV. Reported sexual contact between these two women included oral sex and sharing of sex toys. The newly HIV-infected woman reported that although she never engaged in sex during menses, bleeding during sex had occasionally occurred. The investigators excluded alternative explanations, confirming the patient had never shared toothbrushes or razors with her infected partner, injected drugs, received a blood transfusion nor had had sex with men.

Transmission of syphilis requires only skin-to-skin or mucosal contact which can easily occur in the context of sex between women. In fact, sexual transmission of *T. pallidum*, the causative agent of syphilis, between female partners has been reported.<sup>46</sup> Among WSW who engage in sex with higher risk male sex partners, there may be a higher than usual risk of syphilis acquisition given the recent rise in early infections over the last several years among MSM.<sup>36</sup>

Certain non-sexual risk behaviors including injection drug use (IDU) may be higher among some WSW, and may independently increase risk of HIV acquisition. In one study that included US surveillance for reported AIDS cases from 1980 to 1989, 95% of the 79 women who reported sex with another woman reported current or past IDU.<sup>47</sup> The HIV epidemiologic research study evaluated the sexual behaviors of women who reported prior IDU, had sex with five or more partners in the prior 5 years, had a history of sex with a male sex partner at risk for HIV, or had exchanged sex for drugs or money. In this study, 67 of 871 subjects (8%) have had sex with a woman during the 3.5 years of the prospective follow-up. Most (82%) had a history of IDU. A notable weakness of this study was that information on the HIV status of sex partners was not reported.

## BACTERIAL VAGINOSIS

Bacterial vaginosis (BV) is a condition that occurs when the hydrogen peroxide-producing *Lactobacillus* species that characterizes the normal human vagina are replaced by high quantities of commensal anaerobic bacteria. BV is the most common cause of vaginitis among women of reproductive age, and is associated with pelvic inflammatory disease and preterm labor. BV, though mostly considered significant among women in the context of pregnancy, also increases the risk of STI, including HIV acquisition.<sup>48–51</sup>

The prevalence of BV among WSW is high and vaginal colonization with hydrogen peroxide-producing lactobacilli is low relative to that of heterosexual women matched for age and sexual risk behaviors.<sup>52–56</sup> BV prevalence among WSW in several studies has ranged from 24% to 51%, as compared to 21% for heterosexual STD clinic patients and 9–14% for pregnant women. Although BV is not a classic STI in that a specific microbial precipitant has not been identified, Criswell and Gardner successfully transmitted BV from one woman to another by the transfer of vaginal secretions in early studies of “*Haemophilus*

*vaginalis* vaginitis,” a historical term for BV.<sup>57</sup> Moreover, Marrazzo and colleagues, utilizing rep-PCR to characterize vaginal isolates among 30 monogamous (defined within the time frame of the prior 3 months) female sex partners, demonstrated that 23 of these couples shared identical strains of *Lactobacillus*. Finally, other studies have demonstrated that BV is frequently found in both members of monogamous lesbian couples and that BV concordance within couples has been associated with specific sexual behaviors, including shared use of vaginally penetrative sex toys.<sup>58,59</sup> Taken together, these data strongly support a role for sexual exchange of vaginal microbiota in the pathogenesis of BV among WSW.

Although studies have not demonstrated a consistent positive association, the common practice of oral sex among WSW may play a part in the high concordance of BV among both members of monogamous lesbian couples, as certain anaerobic bacteria that may also colonize the oral cavity are newly identified agents associated with this condition.<sup>59–61</sup> More research is needed in this area.

## TRICHOMONIASIS

One case report of exchange of *Trichomonas vaginalis* has been reported among WSW. Both women in a partnership were infected with *Trichomonas vaginalis* that was found to be resistant to metronidazole.<sup>24</sup> Among 708 new patients attending a clinic for lesbians in London, trichomoniasis was detected in 1.3%, including women who reported no prior sex with men.<sup>39</sup> Presumably, efficient exchange of vaginal fluid between female sex partners should facilitate transmission of this common STI, but data in WSW are lacking.

## Preventive Health

In many industrialized countries, one of the most reliable measures of appropriate provision of preventive health among women is cervical cancer screening. Despite the fact that many WSW accurately perceive themselves to be at risk for cervical cancer, several investigators have reported that WSW are less likely to undergo routine Pap smear screening and preventive gynecologic care relative to their exclusively heterosexual counterparts.<sup>3,62–64</sup> Moreover, as demonstrated in qualitative and quantitative research,<sup>65,66</sup> most women who report same-sex behavior do not believe that they are at risk of acquiring STI from their female partners. This may lead to less frequent use of preventive measures (for example, washing sex toys between partners) or infrequent use of barrier methods (including gloves, condoms, dental dams) for STI prevention. Finally, healthcare providers may neglect to obtain a complete sexual history and thus fail to elicit reports from WSW of higher risk behavior that would prompt STI screening and related prevention counseling.<sup>67</sup>

In Australia, WSW have been a target for routine cervical screening campaigns. A study in the state of Victoria among 409 WSW showed that 66% were considered well-screened, 22% were under-screened, and 12% had never had a Pap smear, while 22% have had an abnormal result.<sup>68</sup> These are representative of

population-based screening rates in Victoria; however, younger WSW in the study were found to be under-screened relative to the women over 40 years of age. Also, women who had disclosed their sexual identity to their primary care provider and had never been advised not to have a Pap test by their provider were more likely to be well-screened. Of concern, 9% of WSW had been advised not to have a Pap smear, generally by their primary care providers.

Three studies in the US have reported low rates of Pap smear screening among WSW. In the Seattle Lesbian Health Study, 95% of the respondents believed they should receive Pap smears annually or every 2 years after a normal smear, but 36% provided a reason for not having done so.<sup>27</sup> Reasons most commonly cited were lack of insurance, adverse experience at prior Pap smear screening, and a belief they did not need it because they were not sexually active with men that was often enforced by physicians. Despite high levels of education and income, women with no prior sex with men were less likely to have ever received a pelvic examination, received their first Pap smear at an older age, and had less frequent Pap smears relative to women who reported prior sex with men. The Boston Lesbian Health Project used snowball sampling to query a national sample of 1633 lesbians.<sup>69</sup> Interestingly, while overall screening rates approximated the general population, 39% of respondents younger than 20 years and 16% of those 20–29 years had never had a Pap smear. A study conducted in New York City that utilized a multilingual population-based survey found that WSW were less likely to have had a Pap test in the past 3 years (66% vs. 80%,  $P<0.0001$ ) and a mammogram in the past 2 years (53% vs. 73%,  $P<0.0009$ ) than other women. Women whose sexual identity and sexual behavior were concordant were more likely to have engaged in healthcare screening practices including Pap smears. In other words, WSW who identified as lesbian were more likely to have received timely Pap tests (97% vs. 48%,  $P<0.0001$ ) than those WSW who identified as heterosexual.<sup>70</sup>

Many WSW (53%–72%) do not disclose their sexual behavior to physicians when they seek care, and disclosures may elicit negative reactions.<sup>64</sup> In a survey of 1086 WSW, only 43% with a clear risk factor for HIV perceived themselves to be at risk.<sup>3</sup> Similar assumptions about HPV acquisition from female partners may place these women at risk for delayed detection of cervical cancer by less frequent or no cervical cancer screening. Finally, WSW who do not also have sex with men may not access venues providing hormonal contraception, thus eliminating another routine opportunity for cervical cancer screening to be sought and/or offered.

## Methods to Reduce Risk of STI Acquisition among WSW

The sexual behaviors of WSW allow transmission of cervicovaginal secretions and blood-borne pathogens, as supported by reports of several STI among women who report sex exclusively with women. Several methods may theoretically reduce risk of STI by preventing contact with infected skin, mucous membranes or

secretions; however, none have been directly studied prospectively among WSW. These measures include washing hands between sexual practices and utilizing rectangular latex barriers known as dental dams (used historically by dentists for endodontic procedures). Dental dams can be placed over the vulva during cunnilingus or the anus during anilingus. Some women may choose to use thin pieces of plastic wrap for the same purpose; however, this material may be porous and potentially less protective. Condoms can be used to cover sex toys used for penetrative purposes. If condoms are used, they should be replaced during exchange of toys from one partner to the other. Latex gloves or finger cots can be used during sex that involves digital stimulation, including vaginal and anal penetration.

Despite evidence supporting transmission of STI among WSW, perceptions of risk and practice of safer sex methods is low.<sup>71</sup> In a qualitative study including focus groups among 23 self-identified lesbian and bisexual women between ages 18–29, among a handful who experienced an STI or BV, practice of measures, including washing hands, cleaning sex toys and use of latex barriers is low.<sup>66</sup> This may be due partly to lack of knowledge of STI transmission between women and overall lack of safer sex messaging by primary care providers and public health advocates that target WSW.

## Conclusions

Women having sex with women are at risk for a full range of viral and bacterial STI and associated conditions, with the available evidence strongly supporting the need for attention to studies of transmission of *C. trachomatis*, HSV, HPV, and BV. While there is a paucity of data on most STI in WSW, relatively solid data do speak to the need for adherence to standard screening guidelines for cervical cancer and *C. trachomatis*.

Healthcare providers should apply their skills in sexual risk assessment to all women, including WSW, with particular effort towards inquiring about potential higher risk male partnerships and illicit drug use. Evidence also supports that while WSW may be knowledgeable about safer sex measures, relatively few practice them. Further research on behaviors and mechanisms of disease acquisition and transmission among WSW, including exploration of higher risk partnerships and behaviors, is needed.

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# Sexually Transmitted Infections in Transgender Persons

Darren Russell

# 101

Transsexualism is defined in the Diagnostic and Statistical Manual (Version IV) of the American Psychiatric Association as a strong and persistent cross-gender identification with a sense of inappropriateness in the gender role of one's biological sex. The definition specifically excludes any concurrent intersex condition. There must also be clinically apparent distress or impairment in social, occupational, or other important areas of functioning. Definitions are problematic with the condition of transsexualism, however, as there remains considerable debate about the terms that are used, both within medical circles, and within the ranks of transgender folk themselves. It is fair to say that the terms in common usage remain in a state of flux.

A “*transgender*” person is one who dresses as, desires to be, has undergone surgery to become, or identifies as a person of the opposite sex. The terms male-to-female and female-to-male transgender persons are used to refer to individuals who are undergoing or who have undergone a process of gender affirmation. “*Transsexual*” refers to individuals who are born anatomically male or female but who have a profound identification with the sex opposite to that assigned to them at birth. It usually refers to people who wish to make the transition, but for one reason or another are prevented from doing so. “*Intersex*” refers to individuals who were born with reproductive organs and/or sex chromosomes that are not exclusively male or female. These individuals were formally referred to as “hermaphrodites,” or as “children with ambiguous genitalia.”

A “*transvestite*” is somebody who cross-dresses. The term may be used as a synonym for the term “*cross-dresser*,” the latter is generally the preferred term. These terms are different from the term “*transvestic fetishist*,” which describes those who intermittently use clothing of the opposite gender for fetishistic purposes, often accompanied by masturbation or other sexual activities.

Some transgender individuals and organizations argue that transsexualism is not a form of transgenderism, but is in fact a specific type of intersex condition. They argue that transsexualism results when the sexual differentiation or structuring of the brain is not congruent with that individual's chromosomal and genital

sex. Many intersex individuals and organizations, however, take offence at this proposition and vehemently assert that intersex and transsexual conditions are totally separate and have very little in common. Perhaps it is best to realize that our understanding of these conditions is evolving rapidly, and is informed by input from the medical, scientific, sociological, and affected communities, and that our concepts are evolving. In practice, it may be best for healthcare practitioners to use the label that the individual him/herself wishes to use, and to realize that the term that is used today may not be the term that is used tomorrow!

For ease of writing, I shall generally use the terms “transgender” and “transsexual” interchangeably throughout this chapter.

## Prevalence

The proportion of the population who are transgender is small. A 1981 report suggests rates of 1:24,000 males and 1:150,000 for females. More recent data from Europe suggest that 1 in 30,000 adult males and 1 in 100,000 adult females seek sex reassignment surgery. If a broader definition of transgender is used (i.e., one that is not dependant on an individual seeking sex reassignment surgery) then estimates suggest that about 1 in 11,000 males and 1 in 30,400 female individuals are transgender. A study from New Zealand of passport holders, published in 2008, showed the prevalence of male-to-female transgender individuals as 1:3639, and the corresponding figure for female-to-male was 1:22,714.<sup>1</sup> The authors point out that these figures are likely to be underestimates.

## Etiology

The underlying cause of transsexualism is unknown, though numerous theories have been proffered. Most transsexuals recall a feeling of dissatisfaction with their biological gender identity, beginning in early childhood. This implies that transsexualism begins very early in life, and current theories suggest that transsexuals are *born*, and not *made*. Transsexuals are generally entirely normal physically, and characteristically lack concomitant



psychiatric illnesses with the exception of depression. One US study reported that 62% of male-to-female and 55% of female-to-male transgender persons were depressed. Thirty-two percent of both groups had attempted suicide.<sup>2</sup> It is likely that this depression is in large part caused by the discrimination suffered by transgender individuals by a society that is largely antipathetic to those with this condition, or who lie even a little outside accepted cultural gender norms. Rejection by family and friends, difficulties in finding and maintaining employment, and difficulties in forming intimate relationships, are all potent factors that may contribute to depression. Genital and other forms of body mutilation may also occur—and may even include auto-castration—especially in those individuals who are denied the opportunity to undergo sex reassignment.<sup>3–5</sup>

## Differential Diagnosis

The diagnosis of transgenderism is usually quite straightforward. By the time an individual has summoned the courage to attend a healthcare professional, they have generally been aware of their condition for many years and have already gained information about transgenderism and its possible treatments. More frequently these days, the Internet is an important source of information and support for transgender individuals. There are several conditions, however, that, on occasion, may be confused with transgenderism. Intersex conditions, cross-dressing, and transvestic fetishism have been mentioned above, and, rarely, *schizophrenia* may present as gender confusion, though the associated thought disorder and other typical features of schizophrenia generally make this condition readily identifiable from transgenderism. It must be remembered, however, that transgenderism may rarely coexist with schizophrenia.

## Treatment

There are increasing concerns with the use of the medical paradigm and the concept of “treatment” when referring to a condition that may merely represent one aspect of the spectrum of the human condition. It was only in 1973 that the diagnosis of homosexuality was removed from the list of mental illnesses in the US, and even more recently in other countries such as China. Likewise, it may eventuate that transgender individuals in the future will be regarded as merely requiring hormone and surgical therapy to return them to their rightful states, and not as a treatment for a psychiatric illness. The management of transgender individuals remains complex and experience-driven, though the World Professional Association for Transgender Health has developed Standards of Care. In most western countries, the emphasis is on psychiatric or psychological assessment and management; in Latin America, however, the emphasis is on the ability to “pass” as the chosen sex, and in Thailand the emphasis is generally placed on cross-living experience.

Treatment typically involves the provision of assessment and counseling initially, followed by the institution of hormonal

therapies (estrogen—and sometimes anti-androgens—in males-to-females, and testosterone in females-to-males). As stated above, the assessment process is generally straightforward in most individuals, though on occasion it can be problematic. Psychiatrists, psychologists, and/or physicians with an interest in transsexualism may carry out the assessment. It may require several interviews over several months and may also necessitate the so-called “real-life experience” when the person lives full-time as their chosen sex. Nowadays, this is commonly done in combination with hormone therapy, though some healthcare professionals prefer to wait some months after the initial interview before commencing such treatments.

Sex hormones exert a negative feedback on the hypothalamus and pituitary gland. Levels of gonadotropin-releasing hormone, luteinizing hormone and follicle stimulating hormone are all regulated or suppressed by levels of endogenous sex hormones. Hormone therapy aims to reduce these levels, leading to a reduction in endogenous estradiol or testosterone production. Furthermore, exogenous estrogen will induce feminization, and exogenous testosterone will induce virilization.

Transgender individuals may or may not choose to undergo surgical genital reassignment (sometimes referred to as “genital realignment”), and this will also be contingent on the availability of surgical expertise, and on the financial resources to pay for these procedures. There are a variety of surgical procedures available, and these are being continually refined. The aim of surgery is to enable the transgender individual to more fully live as their chosen sex, and to function well sexually. In most cases this is now possible. Male-to-female genital surgery is technically simpler than female-to-male surgery, and is generally more successful. The vast majority of post-operative individuals report an overall improvement in their lives and are happy with the decision to have genital surgery.<sup>6</sup>

A Belgian study of 55 transsexuals (32 female-to-male and 23 male-to-female), published in 2005, concluded that after surgery the person's expectations were met at an emotional and social level, but less so at a physical and sexual level. Eighty percent of the participations reported improvement of their sexuality, however. The females-to-males masturbated significantly more frequently than the males-to-females. The majority of participants reported a change in orgasmic feeling, toward more powerful and shorter for females-to-males, and more intense, smoother, and longer in the female-to-male group.<sup>7</sup>

A small minority, however, are greatly dissatisfied post-surgery and regret the decision to undergo it. This reinforces the need for expert assessment initially but points to the fact that it is not possible to determine with perfect accuracy who will, and who will not, be satisfied post-surgery.

## STIs in Transgender Persons

It has been estimated that 60% of transgender people have been infected with some type of STI. Recently, more data have been published on the prevalence of various STIs in transgender

populations. Most healthcare providers still lack information about transgender health issues and in this particular population.

A disproportionate number of transgender individuals find employment in the sex industry because of discrimination in the workplace and subsequent financial hardship. For some transgender individuals in some countries this remains the only means of earning enough money to survive, and to afford hormonal and surgical treatments. Jobs may be lost during the transition process, or after transition it may be difficult for transgender persons to find work if they do not “pass” as their reassigned sex. Because of stigmatization even within the sex industry, transgender persons are more likely to engage in unprotected intercourse.<sup>2</sup> There may also be a financial incentive to engage in risky activities if this means that the person can earn more money to put toward the often-high cost of surgery.

Intercourse may be oral, anal, or neo-vaginal in the post-operative person. In pre-operative male-to-female individuals, and in post-operative individuals with a short vaginal barrel, thigh intercourse (sometimes referred to as “cuissage”) may be practiced instead of vaginal intercourse. Pre-operative female-to-male individuals may sometimes engage in receptive penile-vaginal intercourse, and this may be with heterosexual, bisexual, or homosexual males. Pregnancies would be very unlikely to occur in those individuals on adequate testosterone therapy.

A number of American studies have looked at the prevalence of STIs (including HIV) among transgender persons. A study in Chicago found that 46% of individuals had been forced to have sex, 14% were HIV-positive, 22% had been diagnosed with an STI, and 48% of male-to-female and 85% of female-to-male transgender individuals had had sex without a latex barrier.<sup>2</sup> A retrospective study of the health status of transgender individuals in the US reported a 35% prevalence of HIV for male-to-female transgender individuals. A cross-sectional study from Rome, Italy, assessed the prevalence and incidence of HIV infection in foreign transsexual sex workers and found an overall HIV prevalence of 38.2%, with an observed HIV seroconversion rate of 4.1 per 100 person-years.<sup>8</sup> These HIV prevalences seem inordinately high, but the prevalence in a given population will, of course, vary depending on the prevalence in the general community and on the risk behaviors for the particular transgender population.

A US study published in 1999<sup>9</sup> showed that transsexual inmates were 13.7 times more likely to have a main sex partner while in prison. Furthermore, they were 5.8 times more likely than non-transsexuals to have more than one sex partner while in prison. Given that rates of HIV are nearly always higher in prison populations than in the non-incarcerated population, and that injecting drug use is common, these data give cause for real concern. The provision of condoms and materials for safe injecting use is rare in the world’s prisons and so the potential for the transmission of blood-borne viruses is high. Sexual assault is also a significant risk for transsexual inmates in prisons.

A study from Sydney, Australia, looked at transgender people attending a sexual health service over a 16-year period<sup>10</sup> and of the 40 patients who were identified, 17 (43%) had a history of

sex work, 16 (40%) had injected drugs, and 14 (35%) had had unprotected anal or vaginal sex in the previous 3 months. Twenty (50%) patients had histories of an STI, including three (7.5%) who were HIV-positive. Genital warts and Chlamydia were the most common diagnoses during the study period.

In southern India, a study published in 2008 showed high HIV prevalences among *bijra* (intersex—physiological males who have feminine gender identity, women’s clothing and other feminine gender roles) (18.1%), bisexuals (15.9%), *kothis* (passive receptor) (13.5%), double-deckers (10.5%), and *panthis* (active inserter) (7.6%).<sup>11</sup> Syphilis prevalence was also high among *kothis* and *bijras* (15.8 and 13.6%, respectively).

A recently published study from Mumbai, India, looked at sexual behavior and STIs among 75 male sex workers (24 men and 51 transgender).<sup>12</sup> The HIV prevalence in the group was 33%, but was significantly lower in men (17%) compared with transgender participants (41%). The STI prevalence overall was 60% with syphilis once again being the most common STI apart from HIV (28% overall).

There remains a dearth of data regarding the risk of many other STIs in transgender individuals in many countries. Perhaps the best that can be said is that the risks will vary according to the disease prevalences in the general population, the risk behaviors of transgender individuals, and the ability of such individuals to access healthcare and treatments. In general, though, as for all STIs, marginalized groups are often at the highest risk, and transgender individuals are some of the most marginalized members of society.

## Post-Surgery STIs

There is even less data regarding the risk of STIs in post genital surgery transgender individuals. Following surgery, there are several reasons to believe that the risk of some STIs will be decreased. Access to bacterial STIs such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in the adult biological female is often via the cervix uteri, and post-surgery male-to-female transsexuals lack a cervix. They have, instead, a neo-vagina composed of inverted penile skin (with or without a distal colon loop), and a surgically made urethral meatus. Infection of these tissues with the gonococcus and Chlamydia seems to be very unusual.

I have observed, however, the presence of genital warts and genital herpes in the neo-vagina, but cannot comment on the prevalence of these conditions. It would make sense, though, that these viruses could cause infection in the neo-vaginal tissues, as in the male penile skin. Likewise, syphilis and chancroid, which can cause ulceration in penile epithelium, would be able to cause ulcers in the neo-vagina. I have not observed these conditions, however, in post-surgical transgender persons. There would also be a theoretical reason to believe that post-surgery there would be less risk of the acquisition of HIV infection via receptive penile-vaginal intercourse. Without a cervix (through which most HIV infections in biological women are probably acquired), the male-to-female transgender woman may be at less risk of HIV infection.

Complicating the picture, though, is the presence of traumatic or other ulcers following surgery. The need for frequent neo-vaginal dilatation to prevent the closure of the vaginal barrel can induce traumatic ulceration, or even disruption of the distal vaginal cuff. Similarly, penile-vaginal intercourse can result in trauma, especially as the neo-vagina may be too short and/or narrow for vigorous intercourse, and is not self-lubricating like a biological vagina. This could then allow the ingress or egress of bacterial or viral particles across abraded or ulcerated surfaces.

Where the neo-vagina is of sufficient diameter and length for adequate penile intercourse, traumatic ulceration is less likely to occur. If a colon loop has been surgically added to the distal vaginal cuff, ongoing dilatation is less necessary, and lubrication occurs via normal colonic mucous production. Colonic mucosa, however, *may* be intrinsically less resistant to some sexually transmitted infections than penile squamous epithelium.

It must always be kept in mind that transsexuals, whether male-to-female or female-to-male, may be at risk of STIs via oral or anal sex, and may also be at risk of blood-borne viruses via injecting drug use.

## Conclusion

Transgender individuals have been relatively infrequently studied with respect to STIs, though they may be at higher risk through a combination of various biological reasons and sociological reasons such as stigma, discrimination, and lack of access to healthcare. It is important that healthcare professionals take these factors into consideration when dealing with transgender individuals. Further studies into transgender healthcare issues remain a high priority.

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# Sexual Abuse in Children

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## Introduction

Child sexual abuse (CSA) has been an extremely serious, socially disruptive, psychologically devastating, and medically damaging form of trauma that historically has generated much emotional reactions ranging from denial and rage to malice, exclusion, and victimization of the sufferer in the societies.

The phenomenon of CSA has been well-recognized since as early as the 19th century but it is only recently that there is professional acceptance of its reality. Freud<sup>1</sup> in his lecture on “the etiology of hysteria” had proposed a link between CSA and hysteria. Though in psychiatric research, there were sporadic reports of CSA earlier, a dramatic increase has been recorded since early 1980s. CSA has been a subject of intensive research and clinical study by professionals in the fields of mental health as well as in medical and social sciences. Nevertheless, the entire subject still continues to be shrouded in mystery. It is a complex problem that involves several dimensions ranging from medical, social, psychological, legal, ethical, and moral, in its conceptualizations. Further, there is considerable lack of consensus and clarity in most areas related to the subject that still continues. Since the subject of CSA has been a taboo, societies have often reacted with a so called “ostrich psychology” by either closing their eyes to its presence or by dumping it as a myth or an imagination of the child. Often children reporting CSA were not heard, not taken seriously, shunned, and at times considered to be imagining things that were impossible. Under the circumstances, children were left with no one to confide in and they lived their lives under persistent trauma of abuse. This further led to reluctance of the affected individuals to share their traumatic/painful experiences with the medical health professionals, thus hindering research and further understanding of the phenomenon.

It has also been seen that sexual abuse in children occurs along with other forms of maltreatment, that is, physical abuse, emotional abuse, and neglect,<sup>2,3</sup> making the actual experience of children very complicated, presenting challenges for the clinicians and researchers. CSA contributes to child mortality and morbidity with long standing effects on mental health, alcohol,

and drug abuse, suicide, criminality, risky sexual behavior, eating disorders, and so on that persists well into adulthood. Considering the seriousness of consequences and very high prevalence, the problem of CSA warrants preventive and therapeutic intervention from the very early childhood.

## Definition and Concept

Numerous definitions have been provided for CSA. However, most of these have been fraught with conceptual problems. Any definition of CSA should encompass the following components viz. what is meant by “sexual,” what is the age or developmental level of the participants, and what should be called as “abuse.”<sup>4</sup> For example, Schecter et al.<sup>5</sup> defined CSA “as the involvement of dependent, developmentally immature children and adolescents in sexual activities they do not truly comprehend, to which they are unable to give informed consent, or that violate the social taboo of family roles.” This definition does not clarify about the age, as developmentally immature can be at varying ages depending upon the achievement of puberty; sexual activities can range from use of sexual language to the extreme of sexual intercourse—what is to be termed as amounting to a sexual activity becomes difficult; and indulging in sexual activity can be termed as abuse not only by absence of informed consent or violation of social taboos, but also if it is done for the purpose of sexual satisfaction of the perpetrator. Hence, one can see that the above definition is far from satisfactory. Finkelhor<sup>6</sup> defined “sexual victimization” as, “sexual encounters of children under age thirteen with persons at least five years older than themselves, and encounters of children thirteen to sixteen with persons at least ten years older.” This definition is highly unsatisfactory in terms of not only absence of the concept of “sexual” and “abuse,” but also by the age criteria used. What if the child of age 12 years is subjected to sexual victimization by an adolescent of sixteen years? What if an adolescent girl of 14 years is subjected to sexual assault by a male of twenty years? Hence, despite numerous definitions and conceptual problems, comprehensiveness could not be achieved satisfactorily.

However, the most comprehensive definition can be the one by the Standing Committee on Sexually Abused Children,<sup>7</sup> which states—“Any child below the age of consent may be deemed to have been sexually abused when a sexually mature person has, by design or by neglect of their usual societal or specific responsibilities in relation to the child, engaged or permitted the engagement of that child in any activity of a sexual nature which is intended to lead to the sexual gratification of the sexual mature person”. This definition pertains whether or not this activity involves explicit coercion by any means, whether or not it involves genital or physical contact, whether or not initiated by the child, and whether or not there is discernable harmful outcome in the short term. Also, by this definition, sexual activity between two sexually immature persons (e.g., children) cannot be termed CSA.

Despite numerous conceptual difficulties, if one tries to understand the concept of CSA (and define it), then a practical and broad definition could be—sexual behavior between a child and an adult or between two children when one of whom is significantly older or uses coercion. The perpetrator and the victim may be of the same or opposite sex. The sexual behaviors include touching breasts, buttocks, and genitals (whether the victim is dressed or undressed); exhibitionism, fellatio, cunnilingus, and penetration of the vagina or anus with sexual organs or with objects. Pornographic photography is usually included.

Several forms of sexual behaviors can be seen in school/preschool age children that can range from developmentally expected normal to abusive behavior.<sup>8</sup> Thus, it is important to consider developmental factors while labeling CSA. CSA has to be distinguished from sexual play, which has been defined as sexual activities by preadolescent children of same or opposite sex, separated by no more than 4 years of age, in which there has been no force or coercion.<sup>9</sup>

## Epidemiology

It has been reported that the prevalence of CSA has assumed epidemic proportion affecting children and communities worldwide.<sup>10</sup> CSA has been described as an insidious, persistent, and serious problem that affects 2–62% of women and 3–16% of men as victims depending upon the population studied and the definition used.<sup>11</sup> The true prevalence of CSA is difficult to ascertain due to numerous factors. Broadly speaking, there are two sources of information: (a) data from studies on children who have been sexually abused referred to various agencies like police, social services, and doctors. (b) studies on adult populations exploring into their sexual experiences as children.

Both sources are associated with certain limitations. Official figures from records of medical, legal or social agencies are unreliable as the reporting of the problem is inadequate. In addition, there is generally a poor response rate or lack of cooperation from these agencies, and there is marked restriction of cases to only those that actually come to such sources. The latter source of information makes researchers to rely on questionnaires, inventories

and interviews. These methods of assessment are associated with certain problems viz. reliability of the information provided by the persons, difficulty in being able to corroborate the information from any other source, bias in the information due to the long time interval between the “incident” and the interview, and issues related to the information provided due to its highly emotional and sensitive nature. A problem common to both approaches has been that the definition of CSA has kept on changing leading to difficulty in comparing the data. Apart from the difficulties with regard to definition of CSA, the differences in the data gathering techniques (nature of instruments, who has applied them etc.) and heterogeneity in the age of sample also contributes to the large variability in incidence and prevalence rates of CSA. Laserman<sup>12</sup> has reported that 15–25% of general female population is estimated to have a lifetime history of sexual abuse.

Data from specific agencies’ has shown that there was a sharp increase in cases of CSA during the 1980s<sup>4</sup>; especially in those reported from the UK. Correspondingly, in the USA, the number of suspected and established cases of CSA grew at a rate of greater than 10% per year during the 1980s.<sup>13</sup>

Data from adult population have also shown that CSA is a common phenomenon. Prevalence rates of 10%<sup>14</sup>–59%<sup>15</sup> were reported in the UK-based studies (which were supposed to be representative of the general population) done on the population sample sizes varying from 206 to 1244 persons. Studies from Australia and New Zealand have shown prevalence rate of 22%<sup>16</sup> and 31.9%,<sup>17</sup> respectively. Another study from Australia suggested higher prevalence rates of 33.7% for contact CSA and 42.3% if non-contact forms of CSA were included.<sup>18</sup> Rates from the US have been higher, that is, 38%<sup>19</sup>–65%<sup>20</sup>; though derived from smaller samples. Recent prevalence from US government is a more modest 10.1%; 1.7/1000 girls, and 0.4/1000 boys.<sup>21</sup> Reported rates of CSA in different parts of Europe have varied from 3 to 36 % in girls; 1–15% boys of younger than 16 years.<sup>22</sup>

Finkelhor<sup>23</sup> reviewed 19 retrospective surveys with regard to their experience of unwanted sexual contact as minors, and found a prevalence rate of 1–16% in men and 2–45% in women; prevalence of genital penetration being 1.5% in men and 5% in women. In a review,<sup>24</sup> it was mentioned that cases of CSA in the US rose sharply between 1977 and 1988, leveled off, and registered a decline thereafter. Currently, about 200,000 children with suspected sexual abuse are available to the National Committee to prevent child abuse in US.<sup>25</sup> Between 5 and 10% of girls and up to 5% of boys are exposed to penetrative life sexual abuse and up to three times this number are exposed to any type of sexual abuse.<sup>26</sup>

Data has consistently shown that both boys and girls can suffer from CSA; but the rates are lower (between one-fifth to two-thirds) in boys as compared to girls. Part of it is the problem of reporting, as this could be attributed to reasons of socialized feelings and fear of being called homosexuals. The commonest age range is 8–14 years, though extremes can be present.<sup>27</sup>

CSA cuts across all ethnic groups but American studies have shown it to be probably more common and severe in

Afro-Americans.<sup>28,29</sup> The social class distribution suggests a predominance of lower and middle social class groups. It has been argued that the phenomenon is not uncommon among the higher social class; it is just under-reported.<sup>4,29</sup>

Epidemiological data that is now available suggest that the phenomenon of CSA is prevalent in India. The World Health Organization puts the prevalence figure at around 10%. A study conducted in Mumbai in 1985 reported that 30% of female adults and 10% of male adults had a history of CSA.<sup>30</sup> Nambiar<sup>31</sup> reported that 54% of the rape victims in New Delhi were below 15 years of age. Prevalence rates from Bangalore have been around 15%.<sup>32</sup> Additionally, a significant percentage had been abused by either family members or relatives<sup>30,33</sup>; and differing methods of abuse have been adopted by the perpetrators.<sup>30</sup>

The largest national level survey conducted by the Ministry of Women and Child Development, Government of India, released its data recently.<sup>34</sup> The sample consisted of 17,220 children and adolescents in the age range of 5–18 years selected by a multi-stage purposive sampling design. This is the most authoritative report on child abuse in India. This initiative is particularly laudable as it brought this sensitive issue out of the closet into the public domain in India. The survey revealed that two of every three children were physically abused, more commonly in boys and most often by parents. 53.22% children reported having faced one or more forms of sexual abuse, of which 21.9 % faced serious forms of sexual abuse like sexual assault, making the child fondle private parts, exposing or photographing the private parts of the child. Children on street, children at work, and children in institutional care reported the highest incidence of sexual assault. In half of the cases abusers were persons known to the child or in a position of trust and responsibility and most children did not report the matter to anyone.

During the last decade, the concept of “internet sex offenders” has gained ground, where the victim is targeted through the internet, which is a form of non-contact CSA. A comparison of internet sex offenders with actual sexual molesters showed that there were marked similarities in socio-affective traits and childhood physical abuse.<sup>35</sup>

The rates of CSA do appear to be very high, but need to be interpreted in the light of the methodological shortcomings mentioned previously. Additionally, another important aspect to realize is that the rates are reported to be higher in persons with psychiatric illnesses than in the general population. This assumes importance in the context of psychological aftermath of CSA (discussed later).

## Etiology

To some extent, CSA can be viewed as a social phenomenon, which is linked to general attitudes and practices towards children, and ways in which social relationships are organized and regulated in a particular society.<sup>4</sup> Wherever permissiveness is present, the chances of CSA increase due to increased frequency and intimacy of contact between the adult and the child coupled with decreased

vigil by the caretakers of the child. But, this does not imply that CSA is less and not related to the conservative attitude of the society. Untold or hidden cases may be more frequent in such a conservative society. However, additional and key roles are played by the psychological and “interpersonal network” factors. The ecological model views child maltreatment as a social-psychological phenomenon where factors within the individual, the family, the community, and the culture are embedded.

Finkelhor<sup>6</sup> suggested a “four preconditions” model of CSA that distinguishes between the “motivation to sexually abuse” and three “inhibiting” factors that have to be overcome before abuse actually occurs. The factors under “motivation” basically refer to the abuser’s sexuality. The “inhibiting” factors are (a) internal (e.g., moral values of the abuser/adult), (b) external (e.g., supervision of the child by others), and (c) the child’s own resistance toward the advances of the adult. When these inhibitions are overcome, CSA can occur. Certain occasions where the “inhibitions” are overcome (or get overpowered) could be—use of alcohol by the adult, physical or psychological absence or illness of the child’s mother, emotional insecurity or isolation being experienced by the child etc.<sup>4,6</sup> This psychological model links masculine sexuality and CSA, where the abuser is held responsible for the occurrence of the specific act of abuse.

Another influential theory was the “Family Systems Theory.”<sup>36,37</sup> This theory proposes that the basic problem of the father-daughter incestuous relationship is a dysfunctional family arrangement in which the parents suffer from an “emotional-sexual” conflict (i.e., confusion between conflicts on emotional and sexual levels) that leads to intergenerational confusions related to sexuality. For example, when the child comes to the parent(s) seeking emotional relief/care, he/she gets a sexual response. Two types of family pathology serve to sustain this form of incest.

- (a) Conflict avoidance: Individuals in the family are too insecure to cope up with the event and no one acknowledges what is happening.
- (b) Conflict regulation: Disorganized and argumentative members are open about incest with one another, but hide it from the outside world.

Whatever may be the type of family pathology, not discussing about the conflict or trying to hide the issue/problem from the outside world only tends to worsen the situation, increase chances of re-occurrence, and lead to development of adverse psychological reactions in the child. A recent study<sup>38</sup> highlights the serious issue of blame associated with CSA and how internalization of this blame can cause symptoms in the child. Despite these theories, one should try to understand that both the psychological and family models have their criticisms. However, they do tend to provide a theoretical framework in which the setting and perpetuation of CSA can occur.

It is pertinent to mention certain selected risk factors associated with CSA: maternal youth, parental death, presence of stepfather, harsh punitive tactics, maternal sociopathy, unwanted pregnancy, female gender, older children, and parental h/o childhood maltreatment.<sup>39</sup>



## Sexual Offenders/Abusers

It is equally important to try characterize and understand the persons who indulge in abusing children sexually, that is, the sexual offenders/abusers.

Considerable research is available regarding sexual offenders or pedophiles (a person at least 16 years of age and who indulges in sexual activity with children under 13 years of age).<sup>40</sup> Pedophiles can be of any age. Varying, but high degree of psychological disturbances and psychiatric illnesses have been found in the pedophiles.<sup>41,42</sup> Some authors have questioned the utility of the diagnosis of pedophilia, given that the criteria for specifying who is and who is not a pedophile are not strongly related to one another. They suggest that child molester may be a better term.<sup>43</sup> The adult sex offenders have a high prevalence of personality disorders.<sup>44</sup> Numerous predisposing factors viz. familial, social, academic, and developmental have been implicated for the initiation or perpetuation of sexual offence by these persons.<sup>45–48</sup> Juveniles who commit sexual offenses are a heterogeneous diverse population.<sup>49,50</sup>

Males have most commonly been linked with CSA. However, a most recent report from ChildLine (UK) suggest that the number of children reporting CSA by women has more than doubled in the last 5 years; nearly 25% reporting females to be the offender (<http://news.bbc.co.uk/1/hi/education/8347589.stm>; dated 9 November 2009).

In a review article, presenting meta-analysis of studies on risk indicators for perpetration of CSA between 1990–2003 reported that sex offenders against children were by large no different from sex offenders against adults but they were different from non-offenders on several family factors, behavioral problems, social deficits, sexual problems, beliefs and attitudes.<sup>51</sup> There have been some shocking instances of CSA within the Catholic Church, an issue that has been reviewed and reported<sup>52</sup> with the argument that the priests guilty of CSA are child predators who differ little from other child predators.

## Psychopathology/ Psychological Consequences

Trauma of CSA leads to serious, persistent, and long standing consequences that could persist through adulthood. Though children with CSA manifest psychiatric problems, no specific syndrome has been related to CSA.<sup>53</sup> A host of risk factors leading to psychological problems in CSA have been reported, that is, family-related, abuse related, individual vulnerability, response of others to the event, etc.<sup>54–57</sup> However, every person with a history of sexual abuse does not develop psychiatric symptoms or impairment in functioning. CSA is linked with certain psychological sequelae both during childhood and adulthood. During childhood, emotional disturbances,<sup>55</sup> sexually inappropriate behaviors,<sup>58</sup> suicidal behavior<sup>59</sup> and anxiety problems,<sup>60</sup> and somatoform complaints<sup>61</sup> are some of the common and intensely disabling consequences. A recent study reported frequent association between ADHD symptoms and dissociative disorder in abused children.<sup>62</sup>

From India, surprisingly, the literature on the psychological impact, outcome, and treatment of patients with CSA is meager. Patel et al.<sup>63</sup> had reported on the psychological aspects of 35 children with CSA in a remand home in Mumbai, and found history of psychological problems in 71% of the parents of these children. Additionally, 57% of these children were suffering from some psychiatric illness; commonest being depression.

In a meta-analysis to study association between CSA and self-injurious behavior, it was found that the theory that CSA has central/causal role in self injurious behavior was not supported by evidence. However, the modest association between the two was attributed to their correlation with the same psychiatric risk factors.<sup>64</sup> There is also a greater risk of physical disorders such as headaches, gastrointestinal disorders, somatic symptoms, and panic symptoms in these children.<sup>65</sup>

Although it was mentioned earlier that some children do not manifest with any psychiatric illnesses in the period immediately following sexual abuse, yet this does not support the notion that all is well with these children.

Long-term or adulthood outcome is more complex which can be permanent and even life threatening. Ramifications of the effects of CSA are seen well into the adolescence and adulthood where the presence of psychiatric illnesses is directly or indirectly linked to sexual abuse in the childhood. Adults can manifest with varied emotional and psychological reactions, including socialization, personality disorders, substance abuse,<sup>66</sup> and depression<sup>54,67</sup>; experience adverse social consequences<sup>68</sup>; sexual problems; parenting difficulties<sup>69</sup>; and are at risk for HIV.<sup>70</sup> Research has shown relatively consistent association between CSA and sexual risk behavior, such as sex trading, sexual promiscuity, and early age of first sexual intercourse, but whether this relationship is causal, is not fully understood as yet.<sup>71</sup>

1. There is scant literature on CSA among boys, but psychological consequences such as anxiety, denial, dissociation, and self mutilation are common. Boys may cope with abuse by becoming the angry avenger, the passive victim, a daredevil, or a conformist.<sup>72</sup> In adult populations with psychosis, impact of CSA has been linked with the onset of schizophrenia<sup>73</sup> and also with high level of anxiety among people with schizophrenia.<sup>74</sup> Other consequences of CSA, such as emotional distress, depression, anxiety, dissociation, and Posttraumatic stress disorder, have been found to be linked with mediational factors in the form of self blame, shame, and avoidant behavior. Further, emotional distress appears to mediate link between CSA and alcohol abuse or re-victimization.<sup>75</sup> Thus, there is need to incorporate several methodologies to understand the psycho pathogenesis. Ball et al.,<sup>76</sup> while reviewing the evidence for a causal link between borderline and childhood trauma, concluded in support of a causal relationship particularly in a multi factorial etiological model.

## Physical Consequences

Numerous studies have been carried out to determine the prevalence and relationship of CSA and physical health disorders.<sup>12</sup> CSA has been associated with worse functional disability, more physical symptoms, more physician-coded medical diagnosis, increased emergency room visits and healthcare costs,<sup>77</sup> and increased risk of more behavioral health-risk factors.<sup>78</sup>

Additionally, there is consistent greater association with abdominal pain and gastrointestinal symptoms, pelvic pain and gynecological disturbances, headaches, and physical symptoms of anxiety.<sup>12</sup>

There is evidence to suggest that more invasive sexual abuse, multiple incidents, and longer duration of abuse are associated with worse physical health status.<sup>12,79,80</sup>

## SEXUALLY TRANSMITTED INFECTIONS

A recent study focusing on urban youth suggests that urban adolescents who are abused are at higher risk to develop underage pregnancy, sexually transmitted infections and alcohol/drug abuse compared to non-victimized peers.<sup>81</sup>

The prevalence of sexually transmitted infections in children with CSA ranges from 2 to 7% in girls and from 0.5 to 1% in boys.<sup>82</sup> A recent review reported rates of 1–5% in prepubertal children.<sup>83</sup> The most prevalent STIs are chlamydial infections, genital warts, and gonorrhoea,<sup>84</sup> whereas HIV infection and syphilis are rare.<sup>24</sup>

## HIV Infection

HIV transmission due to CSA has been a topic of research since early 1990s. It is important to remember here that intercourse, as a part of CSA, is essential for its occurrence. Wide variation in the prevalence rate has been reported, that is, 0.3<sup>85</sup>–68%,<sup>86</sup> but the sample size and methodology applied have varied considerably. In fact, certain researchers have shown that CSA did not manifest later on with HIV positivity.<sup>84,87</sup>

The risk of transmission of HIV from a single event of unprotected receptive vaginal intercourse when the perpetrator is infected with HIV is 0.0001–0.003 and the risk of unprotected receptive anal intercourse is 0.005–0.032.<sup>88</sup> During evaluation of a person who has had a potential exposure to HIV and, therefore, may need post exposure prophylaxis, considerations include duration of time that has passed since the potential exposure; likelihood that the perpetrator is exposed to HIV; type of exposure; potential side effects from the therapy; and the patient's adherence to the therapy regimen. HIV post exposure prophylaxis should be initiated as soon as possible after the potential exposure and before 72 hours of the exposure.

## Genital Warts and Human Papilloma Virus (HPV) Infection

A complex interplay between HPV infection, genital warts, and CSA is seen viz. exposure to HPV infection is not necessary

to manifest with warts<sup>89</sup> and there can be a prolonged latency period of up to 5 months for the manifestation of the warts.<sup>90</sup> Studies have shown the presence of HPV DNA, but not genital warts, in children with sexual abuse.<sup>91,92</sup> HPA DNA positivity has been reported in up to 33% of children with sexual abuse.<sup>93</sup> On the other hand, condyloma (or warts) has been seen in 1.8% of children with sexual abuse.<sup>93</sup> It is pertinent to mention here that presence of genital warts in children aged 2–3 years is not always suggestive of CSA.<sup>24</sup> Sexual abuse must be considered in children with anogenital, laryngeal, and oral HPV, but nonsexual transmission like vertical transmission from parents, heteroinoculation from caregivers, and autoinoculation must be considered as well. At times, this differentiation may be extremely difficult, owing to factors like the long incubation period between acquisition of HPV and the development of warts, an unknown incubation period upper limit, the myriad presentation of lesions, and the propensity of lesions to spontaneously remit.<sup>83</sup>

Among HPV DNA, subtypes 6 and 11 have been reported more frequently than subtypes 2 and 3<sup>93</sup> in children with sexual abuse. However, caution should be exercised when attempting to identify HPV DNA in an adult.

## Others

In 33% of children with sexual abuse, abnormal cytology in the form of squamous metaplasia has been reported.<sup>93</sup>

## Arriving at a Diagnosis

Children often do not disclose experiences of abuse for months and years. Caregivers must be sensitive to and cognizant of the medical and behavioral indicators of abuse. Various guidelines have been framed for assessment of children with probable sexual abuse. One of the most comprehensively outlined recent guidance is from the UK by NICE ([www.nice.org.uk/CG89fullguidance](http://www.nice.org.uk/CG89fullguidance)).<sup>94</sup> This guidance has been developed not only to raise awareness but also to help non-specialist healthcare professionals to identify children who are being abused.<sup>94</sup> The NICE guidance lists five points of good practice, that is, to listen and observe, to seek an explanation, recording of information, consider/suspect or exclude maltreatment, maintain appropriate, and complete record/documentation.<sup>94</sup>

Assessments are generally multidisciplinary/multi-specialty, and there is a need for participation of specialized professionals (psychologists, psychiatrists, psychoanalysts, and pediatricians) and relevant others (general practitioners, social worker, health visitor, district nurses, etc.). The non-specialist healthcare professionals tend to act as gatekeepers and source of raising the initial index of suspicion towards the possibility of CSA. If they have a strong index of suspicion, based on their assessment, they should alert the relevant specialists, social services and police for a further detailed assessment and in order to ensure protection of the identified victim.

However, whatever guideline is followed, the basic underlying principle is of elicitation of a comprehensive history and

psychological-cum-physical examination. At the same time, caution needs to be exercised by the examining clinicians. This is especially related to having awareness of the normative sexual behaviors of children. Normal sexual play activities between children should not be taken as CSA at face value. Additionally, to know as to what degree is the sexual behavior of the children with sexual abuse above the expected, a baseline understanding is important.

Along with the above-mentioned issues, the disclosure of CSA is itself compounded by problems of over reporting and under reporting. Over reporting tends to occur if the child is suggestible or if there is evidence/possibility of tangible benefits to the child.<sup>95</sup> Under-reporting can be due to various factors viz. presence of feelings of shame, guilt or fear in the child, wish of the child to protect the abuser(s) with whom a consistent relationship is there,<sup>96</sup> reluctance or avoidance in discussing unpleasant memories related to CSA,<sup>97</sup> fear of having to face negative responses, that is, disbelief, denial, or outright rejection,<sup>98</sup> presence of periods of amnesia (memory loss) for such traumatic events during childhood,<sup>99</sup> and the child tending not to label events of sexual abuse as “abusive.”<sup>100</sup> Additionally, the interview should be conducted with caution, according to the reaction and approach of each health professional, avoiding the victim from repeating his/her story to different professionals as that may intensify the suffering.<sup>101</sup>

Hence, assessment for evidence of possible CSA is not simplistic. It does require a considerable degree of experience, expertise, and tact on the part of clinicians to carry out the same. Pediatricians are generally the first health professional from whom advise/assessment is sought in cases of the possibility of CSA.<sup>101</sup> Although they carry considerable expertise in conducting assessments, concerns have been raised around the inability of some pediatricians to distinguish between normal and abnormal characteristics of the genitalia; especially female genitalia.<sup>102</sup>

Though there are numerous assessment protocols, but probably the most comprehensive assessment schedule for forensic evaluation of children and adolescents with sexual abuse is that outlined by The American Academy of Child and Adolescent Psychiatry. A brief overview of the assessment parameters is highlighted.

## INTERVIEW TECHNIQUES

Several key issues are faced by professionals addressing/evaluating CSA. Therefore, it is imperative that one tries to evaluate them. Some key issues are- trying to find out what happened, evaluation for emotional disorders, considering other possible explanations for these emotional disorders, being aware of related developmental issues, avoidance of bias related to outcome (due to one's preconceptions), being sensitive in perusal, being supportive to family members, and maintenance of accurate records.

The Step-wise interview<sup>103</sup> is one systematic way of assessment. It has, however, not been empirically tested. Its components are: rapport building (i.e., establishing a working therapeutic

relationship), describing any two specific events (i.e., asking non leading, open-ended questions), telling the truth, introducing the topic of concern, free narrative (after the topic of abuse has been introduced), general questions, specific questions (if necessary), interview aids (if necessary), concluding the interview.

Additionally, a detailed developmental history and understanding of family's pattern of interaction is required. Afterwards, the interview may be conducted jointly with parents or caregivers. However, it should be remembered here that individuals from different professional groups emphasize different aspects related to elicitation of CSA.

## ASSOCIATED PSYCHOLOGICAL AIDS

Numerous aids have been utilized for the purpose of elicitation of events and facts related to CSA. However, not every test is useful and the clinician should not take these as a substitute for elicitation of a comprehensive history. Some important ones are as follows:

- (a) Drawings—these have been found useful for assessing and accessing traumatic memories.<sup>104,105</sup> Their utility less in the elicitation of information and emotional aspects that may be suggestive of CSA.
- (b) Anatomical dolls—these are useful for elicitation of a young child's terminology for anatomical parts, and for demonstration by the child. However, these are poor substitutes for history elicitation.
- (c) Psychological testing—certain tests, that is, Rorschach, Personality assessment have been found useful.<sup>106</sup>
- (d) Behavior checklists<sup>107,108</sup> are also available.

## MENTAL STATUS EXAMINATION

Mental status examination is an integral part of evaluation for CSA. This should be carried out as per the developmental level/maturity of the affected person. A detailed observation of the behavior(s) and elicitation of thought process is required. It should be conducted in a relaxed manner, at a neutral location with the help of an audio or videotape. Establishing a good relationship with the child is an integral component, in fact the key to success in terms of elicitation about CSA. However, a certain degree of caution needs to be exercised in that (a) the number of interviews should be kept to the minimum (as multiple interviews may encourage the child to provide incorrect information) and (b) the therapist should not educate or provide new terms or leading statements to the patient. An additional and helpful mode of examination is Play Observation; to be conducted for preadolescents and is a semi-structured examination modality utilizing psychological inputs.

## PHYSICAL EXAMINATION

The physical examination is to be conducted by a mental health professional and pediatrician. This aspect of assessment is valid for children with suspected sexual abuse, and not for adults



with past history of CSA. Traditionally, the examination must be carried out within 72 hours of the molestation, as sperm could be recovered from the adult female genital tract up to 72 hours following penile vaginal intercourse. However, recent recommendations are to bring it down to 24 hours, based on the low yield of forensic evidence from the child's body more than 24 hours after the last sexual contact.<sup>109</sup>

The goals of the examination are identification of injuries that require treatment, to screen and to diagnose STIs, to evaluate (and if possible) so as to reduce the risk of pregnancy, and to document findings of potential forensic value.<sup>24</sup> Three major, specialized forensic techniques that are in vogue are:

- (a) Colposcopy—It is a helpful adjunct. Currently, it is not viewed as an obligatory procedure as most forensically important examination findings are apparent using unaided inspection.<sup>24</sup>
- (b) Foley catheter technique—It is used for hymenal examination. This is a painless procedure. It facilitates the identification of forensically significant physical findings.<sup>24,110</sup>
- (c) Wood's lamp illumination—This test helps to differentiate semen from urine. However, this is to be used to identify suspicious areas or specimens for more definitive forensic testing.<sup>24</sup>
- (d) Confirmatory tests—More intricate tests may be performed for confirming diagnoses of STIs, for example, Gonococcal and Chlamydia cultures, nucleic acid amplification test, enzyme-linked immunosorbent assay, and Western blot for HIV, etc.

A detailed, unaided genital examination is of extreme importance and requires the clinician to be well-versed with anatomical variations of the body, blind to the probable diagnosis of CSA, and experienced in evaluating such cases. This is so as potential bias tends to creep in during examination, if the evaluator has knowledge of history suggestive of CSA.<sup>111</sup> It has been suggested that the prone knee-chest position was the most successful method for detecting hymen lacerations in both pre-pubertal and pubertal girls.<sup>112</sup>

The whole purpose of such a detailed, lengthy and cautious assessment is to ascertain whether or not sexual abuse occurred. Even if CSA is established, certain forensic issues need to be kept in mind and the clinician should ward off these potential confounders, that is, the child making false accusations related to sexual abuse, issues related to whether the child should testify or not? (and what is its credibility and competency), recommendations regarding placement and treatment of children with sexual abuse, and a proper and detailed documentation of the medical report. These issues come into play when there is a high degree of suspicion of sexual abuse, or it is confirmed.

## Treatment

Treatment for CSA is a complicated process. Initially, only adult survivors of CSA received recognition and attention. It is only in the last 15–20 years that specific therapeutic work has been undertaken for managing CSA in childhood. This section focuses in detail on the treatment of sexual abuse during childhood.

**Treatment in primary care:** Firstly and foremostly, it is important to have a welcoming and non-biased attitude toward the child. Hence, rapport establishment is critical at the earliest juncture. Consideration to be given to whether the CSA is acute or chronic, as in acute cases (less than 72 hours after the event), legal processes must have been initiated and completed before proceeding ahead with treatment. Assessments of risks related to physical complications (especially STDs) are mandatory and need to be implemented up to 72 hours of the event.<sup>113</sup>

**Psychological treatment** is complex. Numerous issues need to be kept in mind while dealing with such children.<sup>114</sup> Treatment will be required not only for the affected child, but also for the parents or other family members (who shall be affected by this event). The focus of treatment has to be not only on issues directly related to the abuse, but also to the dysfunctional and problematic relationships associated with it. Numerous practical constraints come into play during the course of treatment viz. the component of confidentiality, secrecy (as desired by the family members), denial on the part of family members (in an effort to ensure secrecy), the legal aspects related to sexual abuse, and liaison with various agencies that are working with the family. However, intervention is helpful because it helps to achieve the break of the abuse and the abusive relationship, and addresses and minimizes the adverse consequences of the abuse.

Different types of psychological interventions have been carried out with some degree of success, including cognitive behavioral therapy (CBT)<sup>115</sup>; dialectic behavior therapy<sup>116</sup>; systems theory based group therapy<sup>117</sup>; and family interventions.<sup>118</sup> For maltreated children, foster care placement can lead to benefits compared with young people who remain at home or those who reunify from foster care, but proper foster care facilities may not be available in many developing nations.

Given the difficulties in treatment, prevention is obviously a high priority. It consists of two approaches—programs catering to high-risk populations and universal education programs.<sup>39</sup> The peri-natal and early childhood programs include the nurse/social worker home visit program where high-risk families are identified and regular visits are made for at least two years. Several trials have demonstrated the efficacy of nurse home visiting<sup>119,120</sup> and Early Start program<sup>121</sup> in reducing abuse in children. Most sexual abuse education programs are aimed at teaching children to avoid sexual victimization or abduction. The efficacy of educational programs in preventing sexual abuse is unclear but it may improve reporting rates.<sup>122</sup>

There is also an issue of future CSA and the prediction of its likelihood as well as prevention. Research has shown that two out three individuals who are sexually victimized will be re-victimized.<sup>123</sup> People, who are re-victimized, show difficulties in interpersonal relationships, coping, affect regulation, and exhibit greater self-blame and shame. Attempts have been made to study cases of CSA for sexual re-victimization in adulthood. It appears that these children exhibit a form of psychological vulnerability determined by factors outside of victim such as family environment or contextual, societal cultural factors including the behavior of

the perpetrator<sup>124</sup> which should be studied. There is need for incorporating risk factors based on evidence to propose future prevention and improve child protection services.<sup>125</sup>

**Drug therapy** is warranted for diagnosable psychiatric morbidity, for example, treating depression. Various forms of non-pharmacological therapies have been tried. The basic aim of these psychological therapies is to provide an opportunity to the child to talk about the abuse and the associated feelings, and gain relief from their inevitable confusion. Furthermore, there is always the need for therapeutic work addressing educational/informative and preventive aspects.

However the degree of psychological disturbance requiring therapy varies from child to child. Hence, the type of treatment and the treatment approach should be individualized.

From India, there is extremely limited literature on treatment that is available. Jain et al.<sup>126</sup> had reported on a case series of five patients with psychiatric illnesses and childhood history of sexual abuse. They reported that psychotherapy (psychological mode of dealing with psychiatric problems) was effective. However there is no literature available to highlight whether any effective treatment (or preventive) strategies for CSA have been developed or implemented.

In relation to treatment and outcome of children with CSA, research tentatively states that some abused children, despite treatment, do not improve or even worsen; the optimal duration of treatment is unclear; dropout rates are very high; it is unlikely that one kind of treatment will suit all children; and boys are harder to treat.

Overall, it can be said that the treatment guidelines and results for CSA are not satisfactory and require a lot of research and clinical input.

## Conclusion

CSA is a common socio-psychological problem that often remains undetected, undiagnosed and untreated. It is associated with a high degree of adverse physical and psychological consequences; some of which can be life threatening. CSA occurs in the background of complex interplay of individual, family-related, and social factors. Assessment for CSA is a tedious and painstaking task associated with a lot of intricacies. In fact, the associated medico-legal and social ramifications complicate the process of evaluation and treatment of CSA. Unsatisfactory assessment and treatment guidelines further compound the difficulties encountered in the process of handling of CSA. The treatment modalities need to be more specific and should be based on explicit conceptual models of psychopathology of CSA and should be based on sound research. Despite the lack of satisfactory treatment for CSA, there is no need to be overly pessimistic in one's approach. It is important to recognize that CSA requires inputs from the psychiatrist at any stage of detection (whether in childhood or in adulthood) so as to alleviate the suffering and manage the adverse psychological consequences arising out of it. Individualized treatment and establishment of a sound therapist-patient relationship still remains the key to success of

treatment of CSA. However, despite a plethora of research from the West, India lags behind in documenting and reporting as well as in intervention studies. Professionals from the medical, social, psychological and legal field should approach, understood and deal with this sensitive issue in an integrated and holistic manner. Nevertheless, sexual abuse in children (i.e., CSA) remains an area where questions definitely outnumber the answers.

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Sexual function is a key indicator of quality of life for many of our male patients. Any clinician who has looked after patients with this group of problems will confirm that many men will suffer anxiety and self-worthlessness when they have sexual dysfunction. This feeling of worthlessness will be shared equally by their sexual partners who may rightly or wrongly blame themselves for their partner's problems.

Sexual intercourse is the most essential and pleasurable behavior and satisfactory sex act constitutes an innate and most important desire of a human being. In simple terms, sexual intercourse depends upon a man being able to feel the sexual desire/drive/appetite, develop and retain an erection long enough to enter into vagina and ejaculate, that is, there should be presence and adequacy of excitement, followed by plateau and orgasmic phase. The problems can arise in any one of the phases of sexual act that includes desire/arousability, excitement, and orgasm. Sexual dysfunction may be considered as a relative term because there may be a vast difference between the expectation and performance. Satisfaction/dissatisfaction with sexual relationship is very subjective and individual in nature. More confusion in terminology and understanding of the problem without a detailed history is likely because many common sexual difficulties such as inability to be completely involved in the sex act, inability to relax, situational factors causing reduced interest in sex, too little foreplay etc. can be interpreted as sexual dysfunction.

**Penile erectile function** is a complex process requiring the combined neurological, endocrinological, psychological, and vascular systems. The etiologies of erectile dysfunction (ED) are therefore, frequently overlapping and multifocal. In order to understand the causes and treatment for ED, it is important to understand the anatomy and physiology relating to erections.

The penis is the male organ that contains the urethra which is the channel through which urine and semen leave the body. The penis consists of a base (closest to the body), the shaft and the glans (that part of the penis farthest from the body). It is attached at the base to the bony pelvis. The shaft or main body of the penis consists of three columns of erectile tissue. It has two side parts, the corpora cavernosa and a central part, the

corpus spongiosum. The central part is close to the surface and surrounds the urethra. The corpora cavernosa are cylinders of spongy tissue each surrounded by fibrous tissue (tunica albuginea). The corpora cavernosa are honeycomb like structures that contain muscle and fill with blood following sexual stimulation. It is this engorgement of the erectile tissue that produces a penile erection. The glans is the acorn shaped region at the top of the penis. It is an extension of the corpus spongiosum. In an uncircumcised man the foreskin covers it.

When the penis is flaccid it is under the control of the sympathetic nervous system which is responsible for reflex or unconscious actions. The blood vessels are narrow and the blood flow is low keeping the penis small. When sexual stimulation occurs the parasympathetic nervous system becomes dominant and this leads to vasodilatation and hence filling of the cavernosal tissue with blood. The increased blood in the penis compresses the veins against the fibrous tissue around the corpora. Because of this pressure less blood leaves the penis and an erection occurs. After ejaculation the penis becomes limp, this is a process called detumescence.<sup>1</sup> The sympathetic nervous system is also essential for ejaculation closing the bladder neck. Damage to these nerve pathways can affect the erectile as well as the ejaculatory mechanism.

### What Causes Erectile Dysfunction?

Erectile dysfunction defines the inability to achieve and maintain an erection adequate for satisfactory sexual performance.<sup>2</sup> Epidemiological studies suggest that 5% of men over age 40, 10% of men in their 60s, and 20% of men in their 70s will have ED.<sup>3</sup> Patients over the age of 80 have a 30–50% prevalence of ED.<sup>4</sup> The cause of male erectile dysfunction can be divided into psychological and physical factors. The former include relationship issues, ignorance, fear of failure, and sexual abuse in childhood or adulthood. The physical factors include conditions which affect either blood vessels and/or nerves, for example, hypertension, diabetes, multiple sclerosis, or pelvic surgery. However, it is good to remember that most men will have elements of both psychological and physical factors involved.



## History and Physical Examination

Sexual and general histories are critical ingredients for diagnosis of ED and for planning therapeutic interventions. The history should include history of concomitant diseases, surgical procedures, smoking, current medications, recreational medication, and alcohol use. The sexual history should differentiate primary ED, in which the patient has had no previous erections, and secondary ED, where function has been lost after previous normal sexual function. Associated ejaculatory problems, diminished libido, and changes in the orgasmic experience also need to be investigated and managed; of crucial importance is the timing of onset, as sudden onset is more commonly associated with psychogenic and post-surgical etiologies, whereas gradual onset is more commonly associated with metabolic diseases, such as diabetes and thyroid disorders. It is important to enquire about the presence of erectile function with other partners, during masturbation, as well as for morning and nocturnal erections. The last successful intercourse should be queried, as well as interpersonal issues, relationship with the partner, lifestyle changes, stress, and possible depression should be assessed. Many men present suggesting that their sexual dysfunction is affecting their relationship. While this may be true in some but in many more cases it will be the breakdown of the relationship which is affecting the sexual function.

ED may be associated with medication use, both prescribed and recreational. The general medical part of the examination needs to elicit history suggestive of co-morbid diseases; these include arterial disease (both central and peripheral), diabetes, renal failure, hypercholesterolemia, and neurological abnormalities, including multiple sclerosis and thyroid disease. A surgical history may reveal surgical procedures associated with ED, including radical pelvic surgery such as abdominal perineal resection, prostatectomy, cystectomy, and pelvic trauma.

Physical examination is focused on the genitourinary system. The penis must be carefully examined to identify abnormalities, such as micropenis, Peyronie disease, or hypospadias. Testicular examination may reveal small, soft, atrophic testes, or absent testes. One of the major reasons for the examination is to be able to reassure the patient as a significant number of men will admit that one of their concerns is about the adequacy of the size of the penis.

## Laboratory Studies

Laboratory studies help identify the co-morbidities associated with ED. Initially these need to include fasting blood sugar levels, a lipid profile and early morning testosterone estimation. Testosterone must be evaluated in the morning, since the diurnal variation in physiological excretion results in the highest values between 0800 and 1000 hours; a late-afternoon testosterone may be low or borderline because of this diurnal variation. Primary or hypergonadotrophic hypogonadism is associated with an elevation in the pituitary hormones, LH, and follicle-stimulating hormone. Most patients, however, have isolated decreases in serum testosterone associated with testicular production deficiencies.<sup>2</sup>

The primary goal of management of ED is to enable the individual or couple to enjoy a satisfactory sexual experience. This involves:

- Identifying and treating any treatable causes of ED.
- Initiating lifestyle change and risk factor modification.
- Providing education and counseling to patients and their partners.

## First-line Therapy

Psychosexual therapy either alone or alongside the couple's relationship therapy is indicated particularly where the patient and/or partner identify significant psychological contribution to the problem or as perpetuating the problem. It is also important to remember that the initial problem may not be with the man but with his partner.

As sex is a subjective experience, it is inevitable that all couples affected by sexual dysfunction have at least some psychological component to their problem. Almost all couples will benefit from simple sex education, and clinicians treating ED should be able to provide this. Helping men to achieve an understanding of their physiological sexual response, the effects of ageing, concurrent disease, and medication may also be important. An improved understanding of the similarities and differences in sexual interest and response in men and women may be beneficial. The clinician should be able to provide simple behavioral advice regarding foreplay, sexual activity, and on the integration of medication into the couple's sexual behavior.

Formal cognitive-behavioral interventions should be provided by appropriately trained and experienced therapists. They may be of some benefit in all men but are probably best used in men with a predominantly psychogenic component in ED. Such interventions are less likely to be beneficial in men with complete ED of predominantly organic etiology. Concurrent use of medication, such as phosphodiesterase type 5 (PDE5) inhibitors, is not precluded in men engaged in cognitive-behavioral therapy, and a combined pharmacotherapeutic-psychotherapeutic approach may be more effective than using these interventions individually or consecutively.<sup>5</sup>

Drugs that inhibit PDE5 increase arterial blood flow, which leads to smooth muscle relaxation, vasodilation, and penile erection.<sup>6</sup> Three potent selective PDE5 inhibitors have been approved: sildenafil, tadalafil, and vardenafil. These medications have proven efficacy and safety both in non-selected populations of men with ED and in specific sub-groups of patients (e.g., men with diabetes and those who have had a prostatectomy).<sup>7-9</sup> The major difference in these drugs is that sildenafil and vardenafil are relatively short-acting drugs, having a half life of approximately 4 hours, whereas tadalafil has a significantly longer half life of 17.5 hours. PDE5 inhibitors are not initiators of erection but require sexual stimulation in order to facilitate an erection.<sup>7-9</sup> It is currently recommended that patients should receive a minimum of eight doses of the highest tolerated dose of a PDE5 inhibitor (taken sequentially) with failure of sexual stimulation at maximum dose before classifying a patient as a non-responder.

Approximately 25% of patients do not respond to PDE5 inhibitors. So-called failure may be due to suboptimal counseling at the initial consultation, which should aim to ensure that the patient understands how to take the tablets properly and to return to the doctor if they are dissatisfied. Cost of drug therapy and reluctance of the partner are frequent reasons for unsatisfactory response.<sup>10</sup> Several measures are described in the literature to salvage patients, clearly identified as non-responders:

- Re-counseling on proper use
- Optimal treatment of concurrent diseases and frequent re-evaluation for new risk factors.
- Treatment of concurrent hypogonadism. It is well-established that testosterone regulates the expression of PDE5 and the responsiveness of PDE5 inhibitors in the corpus cavernosum<sup>11,12</sup> and several studies have shown that patients can be salvaged by treating low or low-normal levels of testosterone.<sup>13,14</sup>
- Occasionally, patients may respond to one drug when another has failed.<sup>15</sup>
- More frequent dosing regimens,<sup>15,16</sup> for example, Cialis.

## SAFETY OF PDE5 INHIBITORS AND DRUG INTERACTIONS

There is no evidence that PDE5 inhibitors significantly increase the rate of myocardial infarction. PDE5 inhibitors do not adversely affect total exercise time or time to ischemia during exercise testing in men with stable angina. In fact, all three PDE5 inhibitors may improve the time to ST elevation.<sup>17</sup>

Organic nitrates (e.g., nitroglycerine, isosorbide mononitrate, isosorbide dinitrate), other nitrate preparations used to treat angina such as nicorandil and recreational drugs such as amyl nitrate (poppers) are absolute contraindications with PDE5 inhibitors. Combined use could result in unpredictable falls in blood pressure and, potentially, catastrophic hypotension. Nitrates are usually prescribed for the treatment of angina; unlike calcium channel blockers and beta-blockers, they convey no prognostic benefit with regard to the prevention of further coronary episodes.<sup>18</sup> As such, it is often appropriate for the physician to review their use in an affected individual and consider their replacement with other anti-anginal agents.<sup>19</sup> Co-administration of PDE5 inhibitors with antihypertensive agents may result in a small additive drop in the blood pressure, which does not usually cause significant orthostatic hypotension. Generally, the adverse event profile of PDE5 inhibitors is not worsened by the concomitant use of antihypertensive medicines.

Alpha-blockers have some interaction with PDE5 inhibitors. Under some conditions, this interaction may result in orthostatic hypotension, and PDE5 inhibitors should be used with caution in patients receiving alpha-blockers. These interactions are more pronounced when PDE5 inhibitors are given to healthy volunteers not previously taking alpha blockers and are rarely of clinical significance when the drugs are not started simultaneously. The Summary of Product Characteristics for alpha-blocking drugs do not carry warnings for use with PDE5 inhibitors.

## Second-line Therapy

### VACUUM ERECTION DEVICES

The principle of vacuum erection devices is simple. A cylinder is placed over the penis, air is pumped out with an attached pump and the resulting tumescence is maintained by a constriction ring around the base of the penis.

- Vacuum devices are highly effective in inducing erections regardless of the etiology of the ED.<sup>20</sup>
- Reported satisfaction rates vary considerably from 35 to 84%.<sup>20</sup>
- Long-term usage of vacuum devices also varies but is considerably higher than for self-injection therapy.
- Most men who are satisfied with vacuum devices continue to use them long-term.
- Adverse effects include bruising, local pain, and failure to ejaculate can occur. Partners sometimes report that the penis feels cold.
- Serious adverse events are very rare but skin necrosis has been reported.

Vacuum devices are contraindicated in men with bleeding disorders or in those taking anticoagulant therapy. They work best if the man and his partner have a positive attitude to them and sufficient time has been spent demonstrating their use.

### INTRACAVERNOUS INJECTION THERAPY

It is the most effective form of pharmacotherapy for ED and has been used for more than 20 years.<sup>18</sup> Providing the blood supply is good, and an excellent result can be achieved in most men. It does not require an intact nerve supply and can therefore be highly effective after spinal cord injuries and after major pelvic surgery such as after radical prostatectomy. However, because of the invasive nature of the procedure it is not acceptable to some patients and their partners, and this may result in poor long-term compliance in those who do try it. Compliance may be a particular problem if the procedure is not explained clearly and fully at first consultation and if adequate support and follow-up visits are not provided.

Alprostadil was the first licensed drug approved for intracavernous ED treatment. Alprostadil can be used in doses from 5–40 µg. The erection occurs typically 5–15 minutes after penile injection and frequently lasts 30–40 minutes, although the duration can be dose dependent. In patients with limited manual dexterity and in some other groups, the partner may be taught the technique. Partner participation in the consultation and training program can be valuable and improve long-term compliance. Some patients prefer to use an automatic injection pen that avoids a view of the needle and can help with the fear of penile puncture.

Efficacy and safety of alprostadil is summarized below:

- Efficacy rates are high—around 70–80% in the general ED population and higher in those without vascular disease

- Once properly taught the procedure has a high reproducibility and high satisfaction rate for both patients and their partners
- Long-term compliance rates however, can be low with as many as 50% of patients stopping in the first 2–3 months
- Careful counseling in the early stages with an assured availability of advice in the first few weeks can improve compliance
- Adverse effects of intracavernous alprostadil include post-injection penile pain (in up to half of the patients after at least some of their injections)
- Other complications include priapism (1%) and fibrosis (2%)
- Contraindications are few but include a history of hypersensitivity to alprostadil, a risk of priapism and bleeding disorders.

MUSE is an acronym for Medicated Urethral System for Erection. Patients are told to void to make sure the urethra is moist, the pellet is inserted into the urethra via a small applicator and the penis massaged. Alprostadil is delivered into the penile urethra and is absorbed through the epithelium into the venous channels of the corpus spongiosum. It reaches the vascular smooth muscle of the corpora cavernosum by retrograde flow through emissary veins, encouraged by penile massage at the time of administration. Use of MUSE results in erections in approximately 30–60% of patients.<sup>18</sup>

- In clinical practice only the higher dosages of 500 µg and 1000 µg are effective
- Application of a constriction ring at the base of the penis may help in some patients,
- Side effects include penile pain (30–40%) and dizziness (2–10%)
- Penile fibrosis and priapism can rarely (<1%) occur
- Urethral bleeding and urinary infection may result from faulty technique

This is a less invasive but also less effective treatment than intracavernosal injection therapy.

### Third-line Therapy

Penile prostheses should be offered to all patients who are either unwilling to consider, or fail to respond to, are unable to continue with medical therapy or external devices. All patients and their partners should be counseled pre-operatively, see and handle all the available devices and if possible speak to other patients who have had surgery.

Penile prostheses are particularly suitable for those with severe organic ED, especially if the cause is Peyronie disease or post priapism. All patients should be given a choice of either a malleable or inflatable prosthesis. Satisfaction rates of 89% were shown in one series of 434 implants. High rates are mainly due to the improved mechanical reliability of the new devices. Five-year survival of these devices is 93% but a revision rate of 7% per year can be expected.<sup>21</sup>

The advantages of penile prosthesis include:

- Long-term efficacy with a high satisfaction rate
- No need for medication
- Improved ability to lead a normal sexual life.

However, patients must be medically fit for surgery and accept potential complications of infection, erosion and mechanical failure which may need re-operation. The initial cost is high but manufacturers do offer a lifetime guarantee.

### Ejaculatory Dysfunction

Ejaculatory dysfunction comprises premature ejaculation, delayed ejaculation, anejaculation, low ejaculate volume, retrograde ejaculation, and painful ejaculation.

All patients should be asked about whether the problem has been lifelong or recently acquired. History taking should include a full history of previous illness, including that of psychotic or depressive illness, any injuries or operations, particularly pertaining to neck, spinal or pelvic injuries, or operations, and any urinary tract operation performed during infancy. Any urinary symptoms should be noted, including assessment of whether the urine flow is good and whether the urine stream sprays (spraying indicates disturbance of normal urethral anatomy). All prescribed medicines and any other medicines or alternative treatments should be noted. It is also important to enquire about alcohol and recreational drug use.

#### PREMATURE EJACULATION

Premature ejaculation (PE) is the commonest male sexual dysfunction and affects approximately 20–30% of the population. Premature ejaculation is the inability to control ejaculation for a “sufficient” length of time during vaginal penetration, which causes distress to the patient and/or his partner. There is no definition of “sufficiency.” For the purposes of scientific studies, a practical definition is an intravaginal latency time of less than 60 seconds. This can be assessed with a stopwatch. More recent literature suggests that more “patient-related outcomes” such as a feeling of control could be a better measure.

Premature ejaculation may be physiological or psychological; it would be primary, lifelong problem or secondary due to physical disorders such as thyroid over-activity, neural or pelvic pathology.

Treatments for premature ejaculation include:

- Simple reassurance
- Ease and squeeze technique
- Topical local anesthetic cream or spray applied 15–20 minutes (but not longer) before sexual contact
- Treatment with selective serotonin uptake inhibitors (SSRIs) (On demand)
- Treatment with SSRIs or tricyclics (Daily)
- PDE5 inhibitors
- Combination topical anesthetic and SSRI



For lifelong PE, the choice lies between topical anesthetics or drugs because reassurance and ease and squeeze are ineffective. At present, the treatment with drugs involves mainly use of SSRIs and the tricyclic antidepressant clomipramine. The main options are paroxetine 20–40 mg, sertraline 50–100 mg, and fluoxetine 20–40 mg. However, side effects of drug treatment can be bothersome: sleepiness at the time of coitus with SSRIs and next day nausea can occur with clomipramine. Drug treatment is evolving, and it has been proposed that the most efficacious drug is likely to be a combination of a 5-hydroxytryptamine (5-HT)<sub>2c</sub> receptor stimulation and a 5-HT<sub>1A</sub> receptor inhibitor. A meta-analysis of the studies of all drug treatments highlighted the limitations of many of the studies on which treatment is now based.<sup>22</sup>

### DELAYED EJACULATION/ANEJACULATION

Ejaculation is considered to be delayed when excessive stimulation is required to obtain orgasm with ejaculation. This is a subjective diagnosis and it is difficult to distinguish when delay becomes pathological. Overall, if the patient complains of delayed ejaculation his complaint should be taken at face value. Anejaculation is the complete absence of antegrade or retrograde ejaculation but with preservation of the sensation of orgasm.

The underlying etiology may be psychogenic, neurogenic, drug-related, or obstructive. Neurogenic anejaculation is seen in spinal cord injury, cauda equina lesions, following retroperitoneal surgery (e.g., lymphadenectomy, aortic aneurysm, horseshoe kidney), following colorectal surgery, in association with Parkinson disease, multiple sclerosis, and diabetic autonomic neuropathy. Drug-related anejaculation may occur with antihypertensives, antipsychotics, antidepressants, and alcohol. Obstructive anejaculation may occur with congenital or acquired blockage of the ejaculatory ducts. There may be failure of development of the prostate or seminal vesicles or following prolonged inflammation of the prostate with fibrosis or when the prostate is replaced by tumor. The condition may occur for social or religious reasons. Some young men learn to masturbate without ejaculation. The consequence of these practices is deconditioning of the ejaculatory reflex, and ultimately this may cause anejaculation. It can also sometimes cause orgasmic pain, hematospermia, and congestive prostatitis.

Often it is not possible to correct any underlying abnormality, for example, after retroperitoneal lymph node dissection, and in such cases treatment results are poor. Provided the lumbosacral segments of the spinal cord are intact, some men are helped by the use of a vibrator applied at the frenulum using 100 Hz and 6000 vibrations per minute. Electroejaculation can be used to obtain sperm and is successful in 90% of men. Prostatic massage has been used to obtain sperm from men with psychogenic anejaculation, and when possible this is logistically easier than electroejaculation, which requires general anesthesia. With lack of ejaculation, an underlying abnormality such as urethral stricture should be corrected. Sympathomimetic drugs such as yohimbine have also been successfully used.

### LACK OF FORCE OF EJACULATION/ LOW EJACULATE VOLUME

Sometimes patients complain of lack of force or low ejaculatory volume. This is a subjective complaint. In overt cases, there is a history of failure of any spurt of ejaculation at the time of orgasm but instead seepage of semen for several minutes after orgasm. The complaint of low ejaculate volume is self-explanatory, although most men have no idea of what normal ejaculation volume should be but nevertheless can distinguish that their ejaculate volume has diminished.

With ageing, there is a reduction in muscle tone of the urethral wall and one of the manifestations of this is reduced propulsion of ejaculation. It also occurs when there has been disruption of the normal urethral musculature, for example, with urethral pathology such as stricture and diverticulum and following substitution urethroplasty. Reduced ejaculate volume may occur because of androgen deficiency. The secretions of the prostate and seminal vesicles are androgen-dependent and ejaculate volume is a good indicator of androgen sufficiency. Also, ejaculate volume may be reduced if there is severe end-stage inflammation of the prostate and seminal vesicles.

### PAINFUL EJACULATION

This is a painful sensation felt in the perineum, urethra or urethral meatus during and sometimes after ejaculation. It most commonly occurs with prostatitis and urethritis and often there is associated painful urination. The condition may or may not be distinguishable from orgasmic pain, which is usually neurogenic in etiology and poorly localized.

### RETROGRADE EJACULATION

Retrograde ejaculation can be caused by any condition that causes failure of bladder neck closure or an increased resistance at the apex of the prostate so that the least line of resistance to passage of semen is back into the bladder. Neurogenic retrograde ejaculation occurs with neurological conditions that cause failure of bladder neck closure or spasticity of the pelvic floor or both. Conditions that can cause this include spinal cord injury, cauda equina lesions, spinal dysraphism, and tethered spinal cord. It may follow disruption of the sympathetic chain by retroperitoneal surgery, for example, following lymphadenectomy, sympathectomy, and aortic aneurysm surgery. It may follow disruption of the pelvic plexus by pelvic surgery, including colorectal and anal surgery. It may occur with generalized neurological diseases such as multiple sclerosis and diabetic autonomic neuropathy (juvenile diabetes).

Various drugs interfere with bladder neck function. These include antihypertensives, alpha-1 adrenoreceptor antagonists, antipsychotics with an alpha-blocking effect, for example, thioridazine and risperidone, and antidepressants.

Anatomical bladder neck incompetence can occur in association with congenital defects of the trigone, including hemitrigone and with ectopic ureters following bladder neck surgery, bladder neck resection, and prostatectomy.

Obstruction at the prostate can be caused by congenital abnormalities such as ectopic ureterocele, urogenital sinus remnants, membranous urethral stricture and verumontanum hyperplasia.

Retrograde ejaculation can be distinguished from anejaculation by the finding of sperm in the postorgasmic urine.

Treatments to restore antegrade ejaculation include the use of alpha receptor stimulating drugs such as ephedrine and amezinium (an antihypotensive agent) or restoration of bladder neck competence by injection of bulking agents or bladder neck surgery. However, the chance of success following the injection of bulking agents or surgical treatment has to be balanced against the risk of causing urinary tract obstruction. Treatments to enable fertility include sperm recovery from the urine, bladder washings and microsurgical retrieval of epididymal sperm and intra-cytoplasm sperm injection.

## Orgasm Dysfunction

Men present less infrequently with disorders of orgasm compared with women. The history given is of a lack of external ejaculation. It should be determined whether there is a lack of orgasm, in which case the problem is one of anorgasmia, or whether orgasm is present but there is a lack of external ejaculation. The patient should be asked about nocturnal emissions. If these occur and if there is no other disease process, then the problem is more likely to be one of psychogenic anejaculation. Retrograde ejaculation is the more likely diagnosis if there is a history of passage of cloudy material in the postorgasmic urine.

Anorgasmia is the inability to reach orgasm; if the spinal cord is intact it is usually associated with anejaculation. After spinal injury and with spinal cord transection, it may be possible to stimulate reflex ejaculation, but there is no sensation of orgasm. Altered sensation and reduced intensity of orgasm often follows radical prostatic surgery. There are two components to this: in part the altered sensation is because of the altered anatomy and the lack of the feeling of the ejaculate passing through the prostate and urethra, but also there is reduced intensity of sensation because of damage to local neural pathways, for example, as a result of spinal cord pathology, following fracture of the posterior pelvis with damage to the pelvis plexus, and after radical pelvic surgery, or radical prostate surgery.

In all cases of ejaculatory problem, the first approach is to treat any underlying disease process, for example, ensure good diabetic control in a man with diabetes, treat prostatitis, etc. Any medication that may be causing the problem should be stopped, if possible, or substituted. Also, treatment depends on the type of ejaculation disorder and whether the man is seeking to enable his fertility, normalize his sexual function or both. In terms of fertility, it is often appropriate at an early stage in treatment to discuss with the patient and his partner home insemination techniques and sperm retrieval techniques, such as microepididymal sperm aspiration, because the treatment of

the underlying ejaculatory disorder may not be successful or may take a long time. In addition, treatment depends on the nature of the ejaculatory problem.

“Libido” is a Latin word meaning “desire, pleasure.” Complaints of “lack or loss of sexual desire” are much more common than those of hypersexuality among men. Many patients presenting with the complaints of reduced sexual desire will actually have other sexual dysfunctions that account for their loss of interest in sex, for example, ED or PE because sexual experience for them is not reinforcing. Equally, the sexual dysfunction may actually lie with their partner, for example, a man loses interest in sex if his partner has anorgasmia or dyspareunia.

Subjects with hypoactive sexual desire are deficient in sexual fantasies and desire for sexual activities. This condition is different from sexual aversion where sexual activity is avoided due to anxiety. Loss of libido or sexual desire can be a lifelong pattern or may occur after a period of good sexual interest or may be only contextual, that is, with a certain partner. Assessment of individuals with hypoactive sexual desire requires full evaluation of medical causes, psychological factors, and relationship issues. There are several conditions or co-morbidities which must be excluded in men who present with decreased libido. These include

- Primary and secondary hypogonadism
- Hypothyroidism
- Pituitary adenomas.
- Mental health problems such as depression, schizophrenia, and substance abuse.

There are also certain commonly prescribed drugs which can lead to decreased desire, which include

- Antidepressants
- Antihypertensives
- Phenothiazines
- Diuretics
- Hypnotics

## Treatment

This is the most difficult of all the sexual dysfunctions to treat. Testosterone has been tried in men and women with inconsistent results. Moreover, masculinizing side effects of testosterone pose a serious issue in females. In a recent study<sup>28</sup> bupropion sustained release has been tried in non-depressed females with low sexual desire—29% of the patients responded to this treatment. Basic treatment involves a combination of psychotherapeutic techniques. Cognitive therapy can be used to change the maladaptive ways of thinking: like the partners may or may not want sex at the same time; or behavior therapy to increase the pleasure out of sexual activity making it a rewarding and pleasurable experience; or marital therapy to improve the relationship between partners. In case of any underlying primary pathology in medical or psychiatric domain, the respective conditions should be appropriately treated. If hypoactive sexual desire occurs secondary to prescription

medicine, then intervention in the form of dose reduction or drug holiday or change of drug or change of treatment strategy to non-drug methods is warranted. However, there are no pharmacological antidotes nor is there any libido pill.

### Summary

Sexual dysfunction involves contribution of biological, psychological, and social factors. Several medical causes such as heart disease, cancer, renal failure, diabetes, neurological disorders, or many chronic medical illnesses can impair sexual function. There are many medications used for common medical/surgical problems like anticholinergic agents, atorvastatin, calcium channel blockers, antihypertensives, anticonvulsants, psychotropic drugs, hypnotics and sedatives, etc. that produce significant sexual dysfunction. It is important to be aware of the problem and explore into all relevant issues so that the problem can be adequately treated. Sexual dysfunction affects the quality of life of individuals and can contribute to secondary morbidity in the psychological or social domains. Physicians have a major role in preventing as well as treating this condition among their patients.

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# Women's Sexual Dysfunction

Verapol Chandeying

# 104

## Human Sexuality

Generally speaking, human sexuality is how people experience the erotica and express themselves as sexual beings. Biologically, sexuality can include sexual intercourse, sexual contact in all its forms, and medical concerns about the physiological as well as psychological aspects of sexual behavior. Sociologically, it can cover the cultural, political, and legal aspects; and philosophically, it can extend into the moral, ethical, theological, spiritual, or religious aspects.<sup>1</sup> In addition, the biological aspects of human sexuality deal with human reproduction and the physical means with which to carry it out. They also deal with the influence of biological factors on other aspects of sexuality, such as organic and neurological responses<sup>2</sup> heredity, hormonal issues, gender issues, and sexual dysfunction.<sup>1</sup>

The ultimate sexual pleasure is the “orgasm.” However, women find it harder than men to experience orgasm because of the increased level of stimulation needed by them to reach orgasm. Majority of women experience orgasm by intense clitoral stimulation, while the orgasm may be harder to achieve by vaginal stimulation. The most sensitive area in a woman's body is the Grafenberg spot (G-spot) which is found in the vagina. If properly stimulated, the G-spot may cause very strong orgasms, even stronger than the ones reached after clitoral stimulation.<sup>3</sup> A number of women are able to experience multiple orgasms even though these are very rarely experienced. The serial orgasms may occur immediately one after another but separated by few minutes.<sup>4</sup>

Women are able to achieve multiple orgasms due to the fact that they do not experience any kind of refractory period as men do after the first orgasm. Theoretically, if stimulation is not interrupted, most women should be able to achieve multiple orgasms. The variety of erogenous zones that a woman has on her body and that can be stimulated are an advantage that women have and men do not.<sup>5</sup> During sexual intercourse, it is usual that men stop the stimulation process in a woman, and this may be one of the reasons why many women do not actually achieve more than one orgasm.

## Basic Differences between Men and Women's Sexuality

A large body of scientific research documents four important gender differences in sexuality. First, men showed moderately higher levels of sexual desire than women.<sup>6</sup> Second, women gained slightly higher than men on general sexual satisfaction within the relationship. Both men and women are most sexually satisfied within an ongoing relationship;<sup>7</sup> however, women may emphasize relational aspects of sexuality slightly more than men,<sup>8</sup> and therefore may fully appreciate the benefits that come from building a stable sex life within an ongoing relationship with a familiar partner. Third, women tended to have slightly higher than men on average level of sexual satisfaction across a wide range of non-orgasmic sexual practices. Given the gender differences in sexual desire, it is very easy to assume that men will “like sex” more than women. That view is supported by one large-scale national survey, which found that men rated almost every one of a list of sexual practices as more appealing than did women.<sup>7</sup> Finally, women's sexuality tends to be more susceptible and capable of change over time. These male–female differences are pervasive, affecting thoughts and feelings as well as behavior, and they characterize not only heterosexuals but lesbians and gay men as well.<sup>8</sup>

For sexual arousal, men and women are different in terms of sexual arousal patterns. Sexual arousal is category-specific in men; heterosexual men are more aroused by female than by male sexual stimuli, whereas homosexual men show the opposite pattern. There is reason to believe that female sexual arousal is organized differently. In contrast to men, both heterosexual and homosexual women experienced strong genital arousal to both male and female sexual stimuli.<sup>9</sup>

## Model of Human Sexual Response

The pioneering research of the human sexual response, and the diagnosis and treatment of sexual disorders and functions, was carried out by Masters and Johnson in 1966.<sup>10,11</sup> Their laboratory-

based observational studies have led to a primary understanding of the physiology of the human sexual response. Later studies have tended merely to confirm or to modify details of the observations they presented in their book, *Human Sexual Response*, over 40 years ago.

The sexual responses of men and women have many similarities in most respects, and have both subjective and physiological components. Subjectively, sexual arousal is how aroused people believe or say they are, while physiological arousal is measured as the extent of physiological response. Bancroft<sup>12</sup> has proposed that at least four major components of sexual arousal need to be independently addressed: (i) sexual appetite or drive, including determinants of both motivation and arousability; (ii) central arousal, including cognitive or attentional factors that define a given stimulus as sexual; (iii) genital responses; and (iv) peripheral indices of arousal, encompassing nongenital somatic, and autonomic changes. Those are the interaction effects between different levels of psychophysiological response.

In general, a woman's sexual responses are triggered by different stimuli from those of a man, and they are more dependent on closeness and affection. When sexual stimulation is maintained, it can lead to a peak or culmination of the induced sexual arousal that causes certain mental (subjective) and physical manifestations (physiologic) that are normally described as the experience of an orgasm. The woman's sexual response is an extremely individual process, and varies in the physical, mental, and emotional reactions to sexual stimulation. The intensity of orgasm also varies widely between individuals, especially women, some can have orgasms so intense and overpowering that they become momentarily unconscious,<sup>13</sup> yet others may have difficulty in recognizing the changes. A number of women have the biological capacity for multiple orgasms.<sup>10,14</sup>

Several models of human sexual response have been proposed by different groups of workers:

### MASTERS AND JOHNSON FOUR-PHASE MODEL

This model proposes four phases, occurring in the same sequence in both sexes; and these are the excitement (E), plateau (P), orgasmic (O), and resolution (R) phases. All phases vary from person to person and situation to situation.<sup>10</sup> This EPOR model—the so-called linear model—is still the standard version followed today.

**(1) Excitement:** Any form of sexual stimulation, including masturbation, manual stimulation by one's partner, oral sex, and fantasy causes the early basic physiological responses of vasocongestion, myotonia (voluntary flexing, involuntary contraction), increased heart and breathing rate, increased blood pressure, and the sex flush. The duration of this phase can last from less than a minute to over several hours. In women, the clitoral shaft gets bigger, the labia majora separate, and the labia minora enlarge while often becoming darker. Some women produce a considerable amount of lubrication at this point, though others only produce a small amount.

Genital vasocongestion results from both parasympathetic and sympathetic nerves releasing nitric oxide and vasointestinal polypeptide which mediate vasodilatation, and acetylcholine which blocks noradrenergic, vasoconstrictive mechanisms and promotes endothelial release of nitric oxide. The relaxation of vaginal smooth muscle permits vaginal expansion, and arteriolar dilatation increases the transudation of interstitial fluid, which promotes lubrication.<sup>15</sup>

**(2) Plateau:** The sexual tension continues to grow as a precursor to orgasm, without a clearly demarked point from excitement to plateau. Everything that happened in the excitement phase continues and becomes more prominent; continued vasocongestion and coloration, continued myotonia, continued increased heart and breathing rate, continued increase in blood pressure, and continued sex flush. The duration of this phase can be very brief, from 2 seconds to a few minutes. During the plateau phase, the clitoris retracts under its hood, while the outer one-third of the vagina becomes especially engorged with blood, creating a structure called "the orgasmic platform."

**(3) Orgasm:** The orgasm is the shortest phase of the sexual response cycle, typically lasting only several seconds, and women can have a slightly longer orgasm than men. During orgasm, the entrance to the vagina contracts rhythmically and the woman experiences waves of intense pleasure, due to rhythmic contraction of the uterus and the orgasmic platform, while the myotonia also causes facial grimaces and twitches in the hands and feet. However, many women may not reach the orgasm phase in every sexual act.

**(4) Resolution:** In this stage, the body returns to its original, nonexcited state. Some of the changes occur rapidly, whereas others take more time. The resolution phase begins immediately after orgasm if there is no additional stimulation.

The refractory period occurs during the resolution phase, and is the time when a man cannot reach excitement, plateau, or orgasm through any kind of sexual stimulation. This period can last from a few minutes to days, depending on his age and frequency of sexual activity, among other things. Women do not experience a refractory period, and they are capable of reaching orgasm from anywhere during resolution. Women have the potential to have multiple orgasms, but a woman may not want to have a second or third orgasm.

### KAPLAN MODEL

In 1974, Kaplan proposed that before the excitement phase (phase E), there should be a desire phase (phase D), and suggested a three-stage model of sexual response: desire, excitement, and orgasm (DEO).<sup>16</sup> After this, Robinson concluded convincingly that the Plateau phase (P phase) was simply the final end of the E phase.<sup>17</sup> Following this Kaplan proposed that the sexual cycle consists of four successive phases, viz., desire, excitement (arousal), orgasm, and resolution (DEOR model), which later on became an accepted model.<sup>18</sup>

## LEVIN MODEL

In this model, the initiating phase of sexual desire (D) was divided into spontaneous desire (D1) and responsive desire (D2), and proposed as the D1D2EOR model, and the P phase was deemed unnecessary as it was actually a phase of increasing sexual excitement and the end of the E phase.<sup>19</sup> The majority of women's sexual desire is actually responsive rather than spontaneous, for instance, a reaction to a partner's sexual interest rather than a spontaneous stirring of her own libido.<sup>20</sup> Moreover, it has been recognized and well-understood that at least one-third of women never experience spontaneous sexual desire.<sup>21</sup> In addition, women may not even experience all of the phases; for example, there may be orgasm and satisfaction without desire, or desire and arousal without orgasm.<sup>22</sup>

## CIRCULAR MODEL

In 1997, Whipple and Brash–McGeer modified the linear model of the sexual response pattern for women, that is, seduction (encompassing desire), sensations (excitement and plateau), surrender (orgasm), and reflection (resolution).<sup>23</sup> This model demonstrated that pleasant and satisfactory sexual experiences may have a reinforcing effect on a woman, leading to the seduction phase and vice versa, on the other hand Basson's circular model emphasizes subjective and interpersonal aspects of emotional and relational intimacy.<sup>20,24</sup> The latter model differs from linear models, and focuses primarily on physical aspects, and has variously modified and included sequentially circular phases of: (i) sexual stimuli with appropriate context, biological, and/or psychological; (ii) subjective sexual arousal which, when sufficiently intense, leads to sexual satisfaction with/without orgasm; (iii) nonsexual rewards; emotional intimacy, well-being, and lack of negative effects from sexual avoidance; (iv) multiple reasons/incentives for instigating or agreeing to sex; and (v) motivation to a willingness to find/be receptive. The spontaneous or innate desire, as reflected by sexual thinking/fantasizing/wanting of sexual sensation per se, may or may not expand the cycle.<sup>24</sup>

## Prevalence of Sexual Dysfunction

A slice of data from the United States National Health and Social Life Survey 1992, for among 1749 women and 1410 men aged 18–59 years, gave figures of sexual dysfunction; 43% for women, and 31% in men. The 43% figure has been questioned because the subject was included into a sexual dysfunction group if the respondent said only “one yes” of seven questions about sexual problems. Later, in an article in *The Journal of American Medical Association* it was stated that its data were not equivalent to a clinical diagnosis.<sup>25</sup>

The National Survey of Sexual Attitudes and Lifestyles 2000 was conducted in the UK among a population of 11,161 respondents aged 16–44 years.<sup>26,27</sup> The questionnaire was based on those used in US survey, and measured the main dimensions of sexual dysfunction, as defined in the International Classification

of Diseases, 10th revision (ICD-10). Persistent sexual problems, lasting at least 6 months in the previous year, were more prevalent among women (15.6%) than among men (6.2%). The most common problems among women were inability to experience orgasm, and painful intercourse, while the main problems in men included lacking interest in sex, early (premature) orgasm, and anxiety about performance. The most common persistent problem among women was lack of interest in sex, and in men it was of early orgasm. Furthermore, short-term sexual problems were relatively common with over a third of men and half of women experiencing at least one sexual problem of at least 1 month's duration in the previous year.<sup>27</sup>

On account of several reasons, Bancroft suggested that there is need to observe caution about medicalization of these clinical issues on account of several reasons: (i) men-women differ in sexuality—women have less need for their sexuality to be influenced by reproductive hormones, and are more susceptible to the repressive effects of social constraints on sexuality; (ii) there is difficulty in predicting when pharmacological effects on sexual response will be beneficial, due to problems in distinguishing between adaptive inhibitions of the response from those that are maladaptive dysfunctions; and (iii) to define when is a sexual problem a sexual dysfunction? Many cases of impaired sexual response or interest in women are psychologically understandable and hence can be considered as adaptive reactions to problems in the sexual relationship, and therefore not dysfunctions.<sup>28</sup>

## Definition of Sexual Dysfunction

The range of sexual problems can be classified as sexual complaints, sexual dysfunction, or disorders. Disorders encompass dysfunction associated with personal distress. Therefore, abnormal function or sexual dissatisfaction can exist without a disorder being present.<sup>29</sup> Because of the broad spectrum of sexual problems, the indicators of severity should also be described such as (i) duration of the problem, lasting more than 1 month or 6 months in the previous year; and (ii) avoidance of sex. The problems of sexual function are relatively common, but persistent problems are much less so.

Help-seeking behavior for sexual problems reflects on the severity of the issues, whereas, the need for professional intervention depends on the patient's perception and on the underlying causes. With regards to obtaining relief for sexual dysfunction, a study in Britain showed that 74.3% of women consulted their general practitioner, while the corresponding figure for men was 63.8%.<sup>30</sup> 4.8% of women sought help at a genitourinary clinic, whereas for men the figure was 9.2%. However, since the licensing of sildenafil more men present with sexual problems at genitourinary clinics.<sup>31</sup>

Previous definitions of women's sexual dysfunction were based on the linear model of human sexual response of Masters and Johnson, and subsequently revised by Kaplan. Traditionally, sexual dysfunction is defined as a disturbance in, or pain, during, the sexual response. However, this is more difficult to diagnose and treat in women than it is in men because of the complexity of the female sexual response. In 1998, the Sexual Function



Health Council of the American Foundation of Urologic Disease revised pre-existing definitions and classifications of Female Sexual Dysfunction.<sup>32</sup> Medical risk factors, etiologies, and psychological aspects were classified into four categories of: disorders of desire, arousal disorders, orgasmic disorders, and sexual pain disorders:

- Hypoactive sexual disorder is the persistent or recurrent deficiency (or absence) of sexual fantasies/thoughts and/or receptivity to, sexual activity, which causes personal distress. Uncommonly, some women may have sexual aversion disorder which is persistent or recurring phobic aversion to, and avoidance of, sexual contact with a sexual partner, which causes personal distress.
- Sexual arousal disorder is the persistent or recurrent inability to achieve or maintain sufficient sexual excitement, causing personal distress. It may be expressed as a lack of excitement or a lack of genital (lubrication/swelling) or other somatic responses.
- Orgasmic disorder is the persistent or recurrent difficulty, delay, or absence of attaining orgasm following sufficient sexual stimulation and arousal, and causes personal distress. This may be a primary (never achieved orgasm) or secondary condition, as a result of surgery, trauma, or hormone deficiencies.
- Sexual pain disorder includes dyspareunia (genital pain associated with sexual intercourse); vaginismus (involuntary spasm of the vaginal musculature that causes interference with vaginal penetration), and noncoital sexual pain disorder (genital pain induced by noncoital sexual stimulation).

Each of these definitions has three additional subtypes: lifelong versus acquired; generalized versus situational; and of organic, psychogenic, mixed, and unknown etiological origin.

In 2004, the Second International Consensus of Sexual Medicine accepted revised definitions of female sexual dysfunction, as given in Table 104.1.<sup>33</sup>

## Causes of Women's Sexual Dysfunction

The basis of desire and perceived arousal in women is poorly understood, but it appears to involve interactions among multiple neurotransmitters, sex hormones, and environmental factors.<sup>34</sup>

Many medical conditions contribute to women's sexual dysfunction (see Table 104.2).<sup>35–38</sup> The microvascular complication may lead to decreased blood flow to the genitalia, causing decreased arousal and delayed orgasm, while polyneuropathy may also contribute to the problem. Arthritis may make intercourse uncomfortable and even painful. It is essential to aggressively treat these conditions and inform the patients of how they can affect sexuality.

There also are various gynecologic causes of women's sexual dysfunction, contributing to physical, psychological, and sexual difficulties, given in Table 104.3.<sup>39,40</sup> The hormonal change during pregnancy/postpartum period may lead to a decrease in sexual activity, desire, and satisfaction, which may be prolonged by lactation. Gynecological surgery such as hysterectomy or vulvar

**Table 104.1:** Revised Definition for Female Sexual Dysfunction from the Second International Consensus of Sexual Medicine

<b>Sexual desire/interest disorder:</b> absent or diminished feelings of sexual interest or desire, absent sexual thoughts or fantasies, and a lack of responsive desire; motivations for attempting to become sexually aroused are scarce or absent; lack of interest is considered to be beyond the normal decrease experienced with increasing age and relationship duration
<b>Subjective sexual arousal disorder:</b> absent or diminished feelings of sexual arousal from any type of sexual stimulation; however, vaginal lubrication or other signs of physical response occur
<b>Genital sexual arousal disorder:</b> complaints of impaired genital sexual arousal, which may include minimal vulvar swelling or vaginal lubrication from any type of sexual stimulation and reduced sexual sensations from caressing genitalia; however, subjective sexual excitement occurs with nongenital sexual stimuli
<b>Combined genital and subjective arousal disorder:</b> absent or diminished feelings of sexual arousal from any type of sexual stimuli plus complaints of absent or impaired genital sexual arousal
<b>Persistent genital arousal disorder:</b> spontaneous, intrusive, and unwanted genital arousal in the absence of sexual interest and desire; arousal is unrelieved by orgasms and persists for hours or days
<b>Orgasmic disorder:</b> despite self-report of high sexual arousal or excitement, there is lack of orgasm, markedly diminished intensity of orgasmic sensations, or marked delay of orgasm from any kind of stimulation
<b>Dyspareunia:</b> persistent or recurrent pain with attempted or completed vaginal entry and/or penile-vaginal intercourse
<b>Vaginismus:</b> persistent or recurrent difficulties with vaginal entry of a penis, finger, or other object, despite the woman's expressed desire to participate
<b>Sexual aversion disorder:</b> extreme anxiety or disgust at the anticipation of or attempt at any sexual activity

**Table 104.2:** Medical Etiology of Women's Sexual Dysfunction

<b>Endocrine</b>	Addison disease, adrenal disorders, Cushing syndrome, decreased estrogen and testosterone, diabetes, prolactinoma, thyroid disease
<b>Gastrointestinal</b>	Irritable bowel
<b>Neurologic</b>	Childhood trauma, epilepsy, head injuries, multiple sclerosis, neuropathies, Parkinson disease, spinal injury, stroke
<b>Psychological</b>	Anxiety, emotional trauma, depression, intra- or interpersonal conflicts, life stressors, physical or sexual abuse
<b>Respiratory</b>	Chronic obstructive pulmonary disease
<b>Rheumatologic</b>	Arthritis, autoimmune disorders, fibromyalgia
<b>Surgical</b>	Colostomy, pelvic surgery
<b>Urinary</b>	Renal failure
<b>Vascular</b>	Coronary artery disease, hypertension, myocardial infarction, pelvic surgery, pelvic trauma, peripheral vascular disease

**Table 104.3:** Gynecological Etiology of Women's Sexual Dysfunction

<b>External genitalia</b>	Bartholin duct cysts, Bartholinitis, Bartholin abscess, clitoral adhesions, episiotomy scar, dermatological lesions (dermatitis, lichen sclerosis, vulvar cancer, vulvar dystrophy), herpes genitalis
<b>Internal genitalia</b>	Atrophic change, cancer, chronic pelvic pain syndrome, cystocele/rectocele, endometriosis, pelvic inflammatory disease, uterine prolapse, uterine fibroid, vaginismus, vaginitis

**Table 104.4:** Medications Likely to Result in Women's Sexual Dysfunction

Antihypertensives	Benazepril, clonidine, lisinopril, methyl dopa, metoprolol, propranolol, reserpine, spironolactone, timolol
Antidepressants	Amoxapine, bupropion, fluoxetine, imipramine, clomipramine, paroxetine, phenelzine, sertraline, trazodone, venlafaxine
Anxiolytics	Buspirone, alprazolam, clonazepam, diazepam, lorazepam
Illicit and abused drugs	Alcohol, amphetamines, amyl nitrate, barbiturates, cocaine, marijuana, ecstasy, methyl-methylenedioxym-amphetamine, morphine, tobacco
Miscellaneous Antipsychotics and mood stabilizers	Acetazolamide, amiodarone, bromocriptine, cimetidine, danazol, digoxin, diphenhydramine, ethinyl estradiol, gemfibrozil, medroxyprogesterone acetate, metronidazole, niacin, phenytoin, ranitidine, perphenazine, prochlorperazine Phenothiazines, Lithium

excision may cause a loss of a psychological symbol of femininity and lead to decreased sexuality. It is important to appropriately treat these conditions and inform the patients of how they may be affected sexually.

Details of medication both prescription and over the counter, as in Table 104.4, should be obtained in order to identify any contributing agents.<sup>41,42</sup> Consideration should be given to dose adjustment, drug alteration, and even drug discontinuation. In addition, use of recreational drugs, alcohol, and alternative therapies should be discussed.

**Assessment:** Involves considerable sensitivity and skill on the part of the physician. It should gradually move from initial phase of screening to a more specific in-depth enquiry exploring into various types of sexual disorders.

## Sexual History Taking

### SCREENING QUESTIONS

The history taking should begin with non-threatening questions. Various examples of questions related to screening

sexual history are:

- Are you currently sexually active? If yes,
- Do you have any discomfort or other problem or any difficulty achieving orgasm? If yes, does this bother you?
- Do you ever experience pain during intercourse?
- Do you have any questions or concerns about your sexual functioning? About your partner's sexual functioning?
- Does that bother you or your partner?

### SPECIFIC SEXUAL HISTORY

Where the patient presents with a specific sexual problem, such as a possible sexual dysfunction or has questions/concerns about sexual functioning, a specific sexual history should be taken appropriate to the problem and concern. Those include history of STI/HIV/AIDS, menstrual, obstetric, perimenopausal, sexual relationship, sexual behavior, and about sexual intercourse etc. The specific sexual history can be explored in depth, and tailored to suit relevant problems such as desire disorder, arousal disorder, lubrication and penetration, and orgasmic disorder.

The several types of sexual problems/queries comprise of:

- (1) myths and misconceptions,
- (2) fear,
- (3) deeper insecurities,
- (4) sexuality in health and diseases,
- (5) sex after surgery,
- (6) alternative orientations, and
- (7) difficult situations.

In addition, two vital questions are suggested at the end of each subset to clarify to the patient, and reminding the neglected point.

- What do you attribute your problem to?
- Is there anything which I have not asked but you would like to tell?

### DESIRE DISORDER HISTORY

Several female reproductive life experiences may uniquely affect sexual desire. These events include menstrual cycles, hormonal contraceptives, postpartum states and lactation, oophorectomy and hysterectomy, and perimenopausal and postmenopausal states.<sup>43</sup> Desire disorder is associated with a wide variety of medical and psychological causes.<sup>44</sup> Questions to ask about desire disorder, (adapted from Ross)<sup>45</sup> are:

- How often do you have sexual intercourse?
- How long have you had the loss of desire?
- How is this problem affecting you? Are you concerned or bothered by it?
- How is your loss of desire affecting your relationship?
- Is it always a problem? Is it a problem only at certain times or in certain situations?
- Has the problem changed over time? If so, how?
- Does anything appear to improve your libido or make it worse?

- Does your partner have any sexual difficulties?
- Do you have any idea about what may be causing your loss of desire? How about your partner's reaction?
- Have you seen anyone else about this problem? If so, what was suggested? What steps were taken?
- Is there anything in your current situation that makes sex unpleasant or difficult with you?

## AROUSAL DISORDER HISTORY

Questions to ask about desire disorder, (adapted from Ross)<sup>45</sup> are:

- How often do you have sexual intercourse?
- How do you and your partner initiate intercourse?
- Do you and your partner usually welcome the idea?
- What happens during foreplay?
- How you feel when your partner inserts his penis?
- Do you touch yourself?
- Have you had any unpleasant experiences with sex?
- Is there anything in your current situation that makes sex unpleasant or difficult with you?

## LUBRICANT AND PENETRATION DISORDER HISTORY

Pain on vaginal penetration for intercourse is a common primary symptom. Questions to ask with regards to lubrication and penetration disorder, (adapted from Ross)<sup>45</sup> are:

- How often do you have sexual intercourse?
- Do you and your partner start with foreplay? How long? Long enough?
- Do you begin to lubricate during foreplay?
- Do you have painful penetration?
- Is penetration successful?
- Is your partner's penis able to remain stiff for insertion? Loses stiffness?
- How do you feel when you or your partner starts the pelvic movement?
- How does your partner feel about your response?

## ORGASMIC DISORDER HISTORY

Orgasmic disorder is parallel in both men and women; it includes early orgasm, delayed orgasm, impaired orgasm, and absence of orgasm. Questions to ask about orgasmic disorder, (adapted from Ross)<sup>45</sup> are:

- Tell me what happened the first time you had sexual intercourse.
- Have you had any unpleasant experiences with sex?
- How did you feel about it at that time?
- What were your physical responses?
- Tell me about your experiences after that.
- How often do you have sexual intercourse?
- What features of the act are you interested in?
- Do you have any problems with lubrication?
- Do you touch yourself?

- How long do you and your partner use for foreplay? Does it satisfy you?
- After you admit the penetration, about how long does it take before you achieve orgasm?
- How do you feel during pelvic movement? Active or passive role?
- How do you feel after sexual intercourse?

There are two common reasons why these questions are not often asked. First, because the clinician may feel uncomfortable with the questions or with his or her level of knowledge of the subject and, second, the amount of time needed for enquiry once the patient senses sincere interest and feels comfortable in beginning a dialogue with the provider. Presence of the partner may also be useful later, once the patient has covered her own concerns.

## Laboratory Testing

With aging, both estrogen and androgen levels decrease in the female, resulting in an increase in sexual pain problems and diminished libido. Although no specific laboratory tests are universally recommended for the diagnosis of women's sexual dysfunction, routine Pap smear and stool examination should not be overlooked. Baseline hormonal profile may be helpful when indicated, including thyroid-stimulating hormone, follicle stimulating hormone (FSH), luteinizing hormone (LH), total and free testosterone, sex-hormone-binding globulin (SHBG), estradiol, and prolactin. FSH and LH can be helpful in assessment of primary and secondary hypogonadism, while decreased estrogen can lead to decreased libido, vaginal dryness and dyspareunia, and testosterone deficiency, as well as raised prolactin, can also cause decreased libido, arousal and tactile sensation. The SHBG level increases with age, and free estrogen level decreases.<sup>46</sup>

## Diagnosis and Management

Women's sexual dysfunction is multifactorial, often with several different etiologic causes contributing to the problem. However, the careful assessment and available treatments can improve the sexual well-being for many women. The diagnosis of women's sexual dysfunction requires the physician to obtain a detailed patient history that defines the dysfunction, identifies causative or confounding medical or gynecologic conditions, elicits psychosocial information, and assesses the patient's goal to set realistic patient expectation, before starting therapy.<sup>47</sup>

Many medical, gynecological, medication, and psychological etiologies are associated with sexual difficulties and problems, which are often underreported and under diagnosed. The patients may feel that sexual problems in the context of disease are not important enough to be mentioned to their physicians, and physicians may feel uncomfortable and sometimes incompetent. Sometimes a sexual problem can be easily improved by diagnosing and treating an underlying problem, such as changing medication use, and treatment of substance abuse. While the complex or multiple aspects of sexual problems can be time intensive, they require specialists (cardiologist, psychiatrist, psychotherapist, sex



therapist, and pelvic physical therapist) with a team approach. In addition, for women with a regular partner(s), the partner needs to be involved in the management of sexual dysfunction.

### Non-Pharmacologic Therapies

The non-pharmacologic options should be the initial treatment for the majority of women because all currently available pharmacologic therapies are of limited efficacy and are associated with potential side effects. The primary focus of the treatment should be confined to optimize health, well-being, and interpersonal relationships.

Some of the non-pharmacological therapies that have been found to be useful are given below:

### Counseling

It is important to counsel that the frequency of sexual activity is not necessarily correlated with sexual satisfaction. Sexual dysfunction only becomes a difficulty when the patient and/or her partner find it to be a problem. Psychological counseling can also play a vital part in treating some women who suffer from female sexual dysfunction, whereas clinical and educational counseling can benefit women in such areas as normal anatomy, the wide variation of the physiologic basis of sexual functioning, coaching in sexual stimulation techniques (foreplay), and the integration of general sexological and disease-specific dimensions. The couple's counseling is effective when there is interpersonal relationship conflict or limited communication.

The counseling could differentiate three diagnostic dimensions. The first are person-related pre-existing factors, such as sexual satisfaction and function, age, body image, and general well-being. The second are the disease-specific implications, which could be summarized under the 8 Ds:

- Danger
- Destruction
- Disfigurement
- Disability and pain
- Dysfunction
- Dysregulation
- Disease load
- Drugs

The third is the patient's and partner's general response to the disease determined by affective response, coping style, body image impact, and changes in relationship dynamics. The differentiation helps the physician to evaluate sexual problems of the female patients with specific clinical conditions in order to facilitate access to recognition and possible treatment.<sup>48</sup>

### Non-coital Behaviors

These include sensual massage and sensate focus exercises. The sensate focus exercise program consists of touching, stroking, kissing, embracing, caressing, and sensual massage during non-

coital love play in ways that are mutually gratifying, first described by Masters and Johnson.<sup>11</sup> It can be used in conjunction with other therapy options such as medication, vacuum devices, etc. The couples allow approximately 30–60 minutes daily (or several times a week) of love play sessions.

Sensate focus may also be used by couples who are not experiencing sexual dysfunction but who want to enhance their sexual relationship. Emphasis is not placed on performance, but on the feelings and sensations of each partner who assumes the active and passive roles at different times during the session. This technique allows patients to know and understand each other's bodies and can be highly effective.

There are several stages associated with sensate focus, according to Masters and Johnson,<sup>49</sup> and as described by Ramage.<sup>50</sup> In the first phase, each explores the other's body without touching the genitals and breasts. The second phase additionally allows exploring genitals and breasts, but intercourse is still forbidden. Focus may be put on different types of touching and stroking of the genitals and the sensations associated with this. Mutual masturbation resulting in orgasm may be an option at this phase of sensate focus. Intercourse is permissible during the final stage of sensate focus exercise, which may start from penetration without thrusting, gentle thrusting or rotating, and thrusting to the point of orgasm. Couples have to consent and agree on the rate of progression through the stages and levels of the sensate focus exercise. It is still crucial for the couple to continue with mutually satisfying love play prior to and during intercourse.

On subsequent occasions, genital touching is allowed, but orgasm is not the goal. Indeed, the goal of sensate focus is to help the partners learn to give and receive pleasure by promoting trust and communication and by reducing anxiety related to sexual performance.

### Kegel Exercises

Kegel exercises, named after Dr. Arnold Kegel, and originally developed in 1948, are exercises of the pubococcygeus muscles which are a major musculature of the levator ani (pubococcygeus, puborectalis and iliococcygeus muscle). This exercise is a method of controlling incontinence in women following childbirth, and now is widely recommended for women with urinary stress incontinence, some men who have urinary incontinence after prostate surgery, as well as people who have fecal (stool) incontinence.

The exercise involves the regular contraction and relaxation of the pelvic floor muscles and is designed to restore muscle tone, reduce overactive bladder symptoms, and to increase sexual satisfaction.<sup>51</sup>

The pelvic floor muscles attach from the pubic bone anteriorly to the coccyx posteriorly and form a bowl-like structure, along with ligaments and fascial tissue. The main functions of the pelvic floor are to provide support for the pelvic organs and prevent incontinence by promoting voluntary closure of the urethral and anal sphincters. Adequate pelvic floor muscle function is a necessary component of bowel and bladder control.

The pelvic floor muscles have been proposed to be active in genital arousal and orgasm in both genders, while their hypotonus may impact negatively on these phases of sexual function.<sup>52</sup>

The strong pelvic floor muscles in women, particularly the ischiocavernosus muscle that attaches to the clitoral hood, are crucial for adequate genital arousal and attainment of orgasm,<sup>53</sup> however, weak or de-conditioned muscles may provide insufficient activity necessary for vaginal friction or blood flow, and inhibit orgasmic potential.<sup>51</sup>

The starting point is aimed at building pelvic floor strength. However, some people have difficulty identifying and isolating the muscles of the pelvic floor. Care must be taken to learn to contract the correct muscles. Typically, most people contract the abdominal or thigh muscles, while not even working the pelvic floor muscles. These incorrect contractions may even worsen pelvic floor tone and incontinence.

#### How to do Kegel exercises?

- Locate the pelvic muscles by stopping the flow of urine mid-stream, and learn how to contract and relax them
- Contract for 1 second and then release, and gradually increase up to 3, 5, and 10 minutes of contractions, 3, 5, and 10 times in a row, and 3, 5, and 10 times a day, respectively
- Doing exercises with a full bladder or while emptying the bladder can actually weaken the muscles, and also lead to incomplete bladder emptying, which increases the risk of a urinary tract infection.

Recently, hypertonus has been found to be a significant contributor to the mechanism of chronic pelvic pain and associated sexual dysfunction. This condition needs physical therapy treatment as an integral component of a multidisciplinary approach.<sup>54</sup>

#### Eros-Clitoral Therapy Device

The Eros clitoral therapy device is approved by US FDA for the treatment of women with sexual arousal disorder. The simple mechanism involves inducing specific clitoral erection using vacuum therapy by self erection inducer device. Therapy over a 6-week period has been shown to be safe and effective in improving symptoms of female sexual arousal, and for enhancing the ability to experience orgasm as assessed by the Female Intervention Efficacy Index,<sup>55</sup> as well as by significantly increasing clitoral and corpus spongiosum diameter, and peak systolic and end-diastolic velocity values, using duplex Doppler ultrasonographic study.<sup>56</sup>

#### PHARMACOLOGIC THERAPIES

The use of pharmacologic therapy should be restricted to women who meet the diagnostic criteria for a sexual disorder, in the form of a sexual problem associated with personal concern, and for whom non-pharmacologic schemes have been demonstrated to be ineffective. Treatment options focus on providing hormonal support and increasing genital blood flow. However, there is no single intervention leading to adequate treatment of women's sexual dysfunction. For example, optimal treatment of diminished

sexual desire may necessitate not only androgen use, but also couple counseling.

#### Estrogen

The mechanism of estrogen's effect on desire is indirect and occurs through improvement in urogenital atrophy, vasomotor symptoms and menopausal mood disorders. This relationship helps predict which patients are likely to respond to estrogen and/or estrogen and progesterone replacement therapy (conjugated equine estrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg daily) in those with symptoms of hypoestrogenism, and may explain why some studies do not show estrogen-mediated improvement in sexual functioning.<sup>57</sup> Hormone treatment did not significantly alter mood ratings, sexual behaviors, or psychophysiological measured sexual arousal.

#### Progesterone

A potent progesterone, such as medroxyprogesterone acetate, is necessary for women with an intact uterus using estrogen; however, it may negatively affect mood and contribute to decreased sexual desire. Monophasic estrogen-progestin therapy in postmenopausal women has a beneficial effect not only on hot flush and atrophic vaginitis but also on sexuality improvement such as sexual desire, dyspareunia, and satisfaction with the duration of penetration.<sup>58</sup>

#### Tibolone

Tibolone is taken orally in the dose of 2.5 mg daily, its metabolites have estrogenic, androgenic, and progestational effects. A small placebo controlled trial in postmenopausal women found tibolone increased vaginal lubrication, arousability, and sexual desire, but did not change frequency of sexual intercourse or orgasm compared to placebo. Tibolone is also effective for the management of osteoporosis, but may be associated with an increased risk of breast and endometrial cancer.<sup>59</sup>

#### Androgen

The 300-microgram per day testosterone patch for 24 weeks increased sexual desire and frequency of satisfying sexual activity and was well-tolerated in women who developed hypoactive sexual desire disorder after surgical menopause.<sup>60,61</sup> One study showed a statistically significant increase in facial hair.<sup>62</sup>

Testosterone in another form, testosterone 1% cream, 10 mg daily for 12 weeks, applied to the thigh also improved sexual self-rating scores by 50% or greater in a statistically greater number of women receiving testosterone compared with placebo.<sup>63</sup>

#### L-arginine

L-arginine, an amino acid, has been touted as the natural Viagra due to the claimed ability to release nitric oxide, causing increased vasocongestion in the genitalia of both sexes. More studies are necessary before conclusions can be drawn regarding any of these products.

Future therapies—a number of products are under research and development for use in women with sexual dysfunction.<sup>64,65</sup>

## Phosphodiesterase Inhibitors

The phosphodiesterase inhibitors (sildenafil, tadalafil, vardenafil) involve adrenergic and/or nitric oxide systems. Sexual stimulation leads to nitric oxide production that in turn stimulates the release of guanylate cyclase which converts guanosine triphosphate to cyclic guanosine monophosphate (cGMP). The cGMP produces relaxation of the smooth muscles of the penile arteries and corpus cavernosum, resulting in increased blood flow into the penis.

These drugs inhibit the metabolism of cGMP, thus prolonging its action. Some evidence suggests that a comparable event may occur in women, as the anatomy of the clitoris is similar to that of the penis. Results from a limited number of placebo controlled studies suggest that the phosphodiesterase inhibitor sildenafil in various doses increases arousal, enjoyment, satisfaction, frequency of intercourse, and sexual fantasies compared with placebo, as well as improving genital sensation, vaginal lubrication, satisfaction with intercourse, and clitoral sensitivity, particularly among postmenopausal women with sexual dysfunction.<sup>66–69</sup>

## Alprostadil

A randomized, placebo-controlled, crossover design study evaluated the effects of alprostadil for the treatment of female sexual arousal disorder. The study compared topical alprostadil solution and placebo, applied to the external genitalia and followed by 30 minutes of visual sexual stimulation. Genital vasocongestion, and physical and sexual satisfaction, were significantly greater than placebo with the 400 microgram dose, but not with the 100 microgram dose. The most common adverse event was mild, transient genital burning typically of less than 1-minute duration.<sup>70</sup>

## Minimizing Sexual Pain

The sexual pain syndrome includes dyspareunia and vaginismus. The alleviation of superficial dyspareunia is the specific treatment of the underlying cause, the use of lubricants, and distraction techniques such as encouraging erotic or nonerotic fantasy, and pelvic muscle contraction and relaxation exercises with intercourse. The management of vaginal dyspareunia is the same as for superficial dyspareunia, whereas the management of deep dyspareunia comprises positional changes so that force is directed away from pain and deep thrusts are minimized, and nonsteroidal anti-inflammatory drugs may also be used before intercourse. However, underlying conditions such as endometriosis, interstitial cystitis, adnexal and bowel pathology should be considered.<sup>71</sup>

Vaginismus is the involuntary contraction of the muscles of the outer one-third of the vagina, and often related to sexual phobias or past abuse or trauma. It can be complete or situational, so that a pelvic examination might be possible while intercourse is not. Vaginismus has a strong psychological component that should be

addressed for successful treatment. Therapy for and counseling of women with vaginismus consists of progressive muscle relaxation and vaginal dilatation with commercial dilators or tampons of increasing diameter placed into the vagina for 15 minutes twice daily. Once the patient can easily accept an equivalent-sized dilator into the vagina, penile penetration by the partner can occur.<sup>39</sup> Success rates approach 90%.<sup>72</sup>

Vulvodynia or vulvar pain syndrome is a chronic, heterogeneous, and multifactorial disease with a high prevalence. This condition typically affects older women while vestibulitis is localized pain provoked by penetration in younger women. The etiology of this condition is complex and remains elusive. An accurate diagnosis requires a comprehensive history, physical examination and targeted diagnostic tests. Although many treatment options have been utilized, a rational therapeutic strategy is still under research. Psychological counseling and group support should be considered in all cases.<sup>73</sup>

## Conclusion

Women's sexual dysfunction is a condition of complexity in both diagnosis and treatment. Numerous women suffer from sexual dysfunction; however, it is unknown how many women are successfully treated. Though there is no permanent cure, all kinds of sexual dysfunction can be controlled and improved with treatment. To date, there are no pharmacological agents proven to be beneficial beyond placebo in enhancing orgasmic function in women. Until recently, there has been limited clinical or scientific research in the field of sexual dysfunction in women. Although some progress has been made, additional research is needed to assess treatment efficacy and establish standard treatment guidelines.

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### Is Sexuality Education Necessary?

Children are naturally curious about sex and bodies but frequently get a message very early in life that this is not an area in which questions are welcomed or where they will get honest and clear answers. Research with Australian parents has indicated that they believe they are communicating well with their children<sup>1</sup> and are keen to provide information. At the same time parents are also wishing to give moral and safety messages<sup>2</sup> in the face of a perceived tidal wave of conflicting sexual values. Education from parents can also be complicated by the embarrassment experienced by many adults in discussing an area which is sensitive or taboo. In many cases, parents have grown up in times when families did not talk about sexuality, and they now want to do things differently. It is therefore not surprising that many young people grow up without getting reliable factual information, or an opportunity to reflect on managing sexuality related issues supported by adults close to them. In the past this might have meant that they remained ignorant, with all the potential for danger that entailed, but today young people have so many other sources of sexual messages and information that this is not likely to be the case. Internet sites, advertising, film and television, as well as the ever-present option of sharing knowledge among peers, means that young people learn a lot about sex, and more than ever need support and guidance to make sense of it all.

Good sexuality education is far more than just imparting knowledge and making sure young people have factual information if we are to prepare them for safe and enjoyable adult sexual lives.<sup>3</sup> The cognitive development of young people throughout adolescence means that they are progressively less willing to accept what their parents tell them is right or wrong. At this stage of life they prepare for adulthood by canvassing the views of many others, especially peers, in order to develop a personal ethic and make sound decisions for themselves. The World Health Organization (1998) has set a broad agenda of the life skills needed for young people to maintain their sexual health. These are the ability to:

- make sound decisions about relationships and sexual intercourse and stand up for those decisions

- deal with pressures for unwanted sex or drug use
- recognize a situation which may turn risky or violent
- know how and where to ask for help and support
- know how to negotiate protected sex and other forms of safe sex when ready for sexual relationships

Detailed knowledge about human anatomy and physiological changes or various sexually transmitted infections is only a small part of the learning that young people need to put such skills in place. Yet, too often it is the factual knowledge that is seen to stand alone as “sexuality education” because some of the other areas are too challenging for parents and teachers alike.

### Partnerships—Who should be Involved in Sexuality Education?

Parents and caregivers are the first teachers of children learning about sexual development and relationships. Even if no formal education takes place, they are role models for their children and inevitably convey messages about the acceptability and appropriateness of ideas and behaviors. However, actual discussions that answer children’s questions honestly and factually from an early age provide an important foundation for ongoing education. As children move into adolescence, those parents who have established good communication with their children have an opportunity to put their views and values in a way that young people perceive as non-authoritarian and therefore valuable. Parents and caregivers can also play a role in assisting young people to find other reliable and independent sources of help such as introducing them to a good medical service. Whatever they are able to contribute to the sexual development and decision making of their growing child is extremely important. The lessons learnt about relationships and the sources of support found within the family may also have a strong influence on the adolescent’s drift towards a particular peer group,<sup>4</sup> which leads us to what is likely to be the second greatest determining factor of an adolescent’s sexual choices, their peers.

Peers are an inevitable source of information for young people and are a readily available one which they experience as being



trustworthy and accessible.<sup>5</sup> Peers also act as the standard setters for what are deemed to be acceptable sexual behaviors and conduct of relationships, as acceptance and connection with peers are highly prized by the developing adolescent. While information that they have may be limited or incomplete, their genuine empathy for their fellows and their ability to offer realistic advice and support can be valuable assets.<sup>6</sup> Many educators despair of young people privileging information from peers over that given by more authoritative sources. As we educate young people in schools we are also educating peers who have the capacity to remain supportive. Peer education programs recognize this resource and can capitalize well on their credibility.<sup>7</sup>

While home and peers remain the most influential spheres of influence in a young person's social and sexual lives, school then becomes an essential third partner with a different and important role to play. School-based education ensures there is a place for guided discussion and critical reflection about sexual choices, skills practice and situation rehearsals, hearing others' views and decision-making processes, and critiquing and understanding the range of influences.

Also involved in sex education for young people may be healthcare professionals who have expert knowledge of some key curriculum areas and also have the ability to encourage young people to seek medical advice when it is needed. Healthcare professionals have been generally used in an ad hoc way in schools<sup>8</sup> with misunderstandings on both sides about how much of the curriculum they should teach. Their most valuable contribution to school-based programs is enabling young people to meet a local nurse or doctor in the safe environment of a classroom. This is likely to make it easier for young people to follow-up the contact individually when the need arises. Outside agencies taking classroom lessons should be limited as they cannot replace trained and committed teachers who have an ongoing relationship with their students in teaching the entire curriculum.

The fourth potential member of the partnership in some cases may be the church which would take a role in contributing to education in the moral aspects of sexual decision making and behavior. While for many this moral dimension would be seen as a religious one, other young people develop a personal morality from many alternative sources of which the church may only be one.

## What is Good Sexuality Education?

The value of comprehensive sexuality education in schools should no longer be a matter of debate. While young people attend school they present an opportunity for education that will not be there at a later stage when they are out in the workforce and the evidence that sexuality education works is now very strong. In December 2009, the United Nations Educational, Scientific, and Cultural Organisation released the final version of their *International Guidelines on Sexuality Education*. The guidelines are in two parts and the first covers the evidence base for this work with a review of 87 program evaluations that the authors deemed

comparable and that had documented demonstrated effects on the sexual behavior of participants. Additional 11 studies of abstinence-only school programs were analyzed separately.

Of the 87 core projects from all over the world, more than a third were found to delay the initiation of intercourse, about a third decreased the frequency of intercourse, more than a third decreased the number of sexual partners, and nearly all studies demonstrated an increase in knowledge. There was very strong evidence that more than one third of the programs increased condom or contraceptive use and that more than half reduced sexual risk taking. The abstinence-only programs however, were less successful with only two showing any evidence of delaying sexual intercourse or reducing the frequency of sex, and one reducing the number of sexual partners. It is clear that sexuality education, if it is carried out in particular ways, can make a difference to the safety and wellbeing of young people.

The evidence drawn from this meta-evaluation is used in the second part of the guidelines to distil four elements of best practice. These are the key elements that are commonly found accompanying measurable improvement in student knowledge and behavior, and the ones that most deserve our attention and advocacy to preserve an area of education which is often contested or under threat.

The first two elements are connected and are probably the most challenging for those working in a school setting because they are about time allocation. Good programs require at least 12 sessions and need to be sequential over several years. It is well-established that young people go through puberty on differing timetables and that they become sexually active at different times.<sup>9-11</sup> Covering this range of needs takes time and persistence but is important if young people are to have access to education when they most need it.

The third element of best practice is outside the classroom and requires the support of, and supervision by, school managers. A whole school commitment to the values that privilege sexuality education as essential for young people requires strong and committed leadership. It cannot be just the work of one passionate teacher who may face criticism from outside sources. Teachers move on for various reasons and it is important that schools maintain a consistent program over time that is part of the regular curriculum. To encourage school leadership to support such programs it may be vital to have a centralized strong government policy which leaves individual schools in little doubt about their responsibility to educate the young people in their care. It can be difficult for individual schools to take a stand and face possible public criticism without the clear authority that a government policy brings.

The final element of best practice is about teachers. Essential to the conduct of best practice sexuality education are capable and motivated teachers who receive quality training. Many times sexuality education is not seen as a prestigious area of education and, despite its importance in the lives of pupils, it is given to a reluctant teacher who is asked to do this work without being trained to do so. Good teacher training is essential to make teachers confident, not just in their knowledge, but in using the

discussion-based methods that help students formulate ideas and develop new skills.

These guidelines also map the territory of good sexuality education to provide a sound basis for curriculum development and classroom planning. The content areas are:

- Relationships, including those with families and friends as precursors to romantic relationships, long-term commitment, marriage, and parenting.
- Values, attitudes and skills, including norms and peer influences, decision making and refusal and negotiation skills.
- Culture, society, and human rights, including the role of the media and gender-based violence and other harmful practices.
- Human development which covers not just anatomy and physiology but also reproduction, the changes of puberty, body image, and bodily integrity.
- Sexual behavior and responses across the life cycle.
- Sexual and reproductive health, including pregnancy and sexually transmitted infection (STI) prevention.

A program which picks up elements of all these areas, begins early, is carried out in a sustained manner and is practical and non-judgmental in its approach will serve young people well.

### What is Age-Appropriate Sexuality Education?

Not all elements of a comprehensive program will be taught at all levels of a child's development and most will be adapted to what children can understand. For example, the area of relationships will focus on family and friends in the early years and move to romantic relationships as that interest develops in the growing adolescent. Age-appropriate sexuality education is education that is relevant to the individual student's physical and cognitive development at the time.<sup>3</sup> Identifying what is age appropriate brings challenges. Not all students of any given age are the same. In any classroom there will be a wide range in the students' growth, interests, and needs, despite sharing the same age. Additionally, child and adolescent sexual development is not wholly biologically determined. As much as bodily growth imposes a general guide of what young people will need, the types of information and skills they need are also influenced by the social context, time, and place in which they live. There is no "universal" 12-year-old or 16-year-old, with corresponding universal educational needs. This is an area where lifelong learning will be as important as anything learnt in school.

That said, programs must attempt to gauge students' needs and concerns to inform any program's content and teaching methods and acknowledge and respond to cultural differences. This needs assessment process, an ongoing one by the teacher who may use methods such as anonymous question box, classroom discussion to assess students' maturity, brainstorm activities around the meaning of different words, and personal one-to-one discussions.

### Respecting Cultural and Religious Diversity

Being respectful of cultural and religious differences should not override a basic assumption that there is some core educational territory which must be covered for all young people.<sup>3</sup> When any of this basic information seems to be in conflict with the cultural or religious beliefs of some students, then it is important to find ways of teaching that address some of those concerns.

Addressing these issues may take many forms. Reassurances about the research evidence showing that sexuality education does not lead to increased sexual activity<sup>12</sup> are valuable. So is information about the broad nature of sexuality education beyond just sexual intercourse to relationships, decision making, and other health issues. Sometimes a person with health or religious expertise may be the best person to present some material. Single sex groups may also make education in sensitive areas a bit more comfortable.

Students may need to be reminded that while everybody is entitled to their own set of values and debate them respectfully in a constructive way, values and beliefs which compromise the safety and wellbeing of other students should not be expressed within a classroom. Homophobic, racist, or sexist remarks should never be tolerated in a sexuality education classroom.

### Respecting Sexual Diversity

Research has shown that around 10% of young people experience same sex attraction, often while they are at school.<sup>13,14</sup> While this does not automatically indicate any particular sexual identity, all of these young people are struggling with a possibility which they may be reluctant to share with anyone else for fear of rejection. Same-sex attracted young people experience high levels of stigmatization, violence, and abuse, particularly in schools.<sup>13-15</sup> It is not a safe strategy to assume that as a teacher you can identify young people in this category and develop education based on their needs.

All young people need to hear positive and reassuring messages about homosexuality as a natural and healthy way for some people to be, and to have inclusive messages built into all areas of the curriculum. For example, if the issue of STI transmission is being covered then discussing it in terms of specific sexual practices rather than as "intercourse between a man and a woman" would be an inclusive message. Another way to be inclusive is to use the term "partner" in discussions about relationships so that everybody can experience their issues being reflected in the discussion.

### Respecting Young People with a Disability

All children and young people need sexuality education. Some students, depending on the type of disability, will require even more efforts to ensure their reliable sexual learning. In the past, a degree of protectiveness around students with disabilities may have meant curtailing opportunities for exploring this side of their development. For example, even though people with an

intellectual disability can experience STIs, unplanned pregnancy, and sexual abuse at higher rates than the rest of the population, they do not always have the opportunity to learn protective behaviors. Students with learning disabilities should still receive information that is relevant to their age, for example, information about puberty, however, the teaching methods may need to vary to accommodate the disability. The goal should always be to find an appropriate way to ensure these students are not excluded from sexuality education.

## A Holistic Approach

Young people will educate themselves about sexual matters irrespective of whether or not they receive formal education. They live in social worlds that give them access to information in far greater volumes than in the past. The issue of accessing age-appropriate and authoritative sexuality education has now become one of human rights.<sup>16</sup> Whole schools can work together outside classroom lessons to teach and reinforce respectful relationships between the sexes and positive role modeling around respectful and appropriate language and behavior. This gives students an excellent grounding for safe and satisfying adult relationships in the future. Peer groups which are well-informed and well-supported play a key role in a cohort of emerging adults who in turn support one another. Families which see the territory of sexuality education as one for informal discussion and lifelong learning also contribute well to the development of young people. Sexuality is more than a range of behaviors and a body of knowledge. It is a core part of being human and is best nurtured by a range of partners who can make a unique contribution to the future of a young person.

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## Introduction

In most cultures, sexual adequacy is the benchmark of masculinity, virility, personal adequacy, and fulfillment.<sup>1</sup> Semen loss related psychological distress has been reported consistently, both in European as well as Asian cultures. While Ayurveda cautions against the loss of semen and argues for its conservation, in the West emphasis has been on defining the adverse physical and psychological sequelae of seminal loss. Dhat syndrome, a term coined by Wig<sup>2</sup> is deemed to be a common culture-bound preoccupation regarding semen loss among patients in the Indian subcontinent. This condition, strictly speaking, is not a psychosexual dysfunction but a culture-specific, sex-related disorder.<sup>3</sup> The presented symptoms in this syndrome have a hypochondriac quality and usually include general weakness, lack of energy and concentration, impaired sexual functions, and vague somatic troubles, all associated with an anxious and dysphoric mood state; typically attributed to the imagined loss of semen in urine or to natural nocturnal emissions.<sup>4</sup> Despite the patient's assertion and concern about the passage of semen in urine, there is no objective evidence of presence of semen in the urine.<sup>5</sup>

## Evolution of Concept

Ayurveda system teaches the physiology of the production of semen, based on the central idea that there are seven essential constituents of the body (the seven *Dhatus*: chyle, bile, blood, flesh, fat, bone marrow, and semen) produced through a cycle of successive internal cooking and transformations. After ultimate distilling, the most concentrated and hence the most precious elixir among the constituents of the body is semen (*dhatu*). In *Charak Samhita*, disorders of *dhatus* have been elaborated and a syndrome resembling modern day Dhat syndrome by the name of *sukrameha* (*shukra* = sperm + *meha* = passage in urine) finds a prominent place. In *Susruta Samhita* and Ayurveda, loss of semen in any form leads to a draining of physical and mental energy and vitality.<sup>1,6</sup> This is further reinforced by the belief enshrined in religious scriptures according to which 40 meals produce one drop of blood, 40 drops of blood make one drop of bone marrow, and

40 drops of bone marrow form one drop of semen.<sup>7</sup> Considered in this religio-cultural perspective that is deeply ingrained in the minds of common folk in India, psychogenesis of the Dhat syndrome is easy to comprehend.<sup>1</sup>

## Epidemiology

Dhat syndrome is quite common in the natives of the Indian subcontinent.<sup>8-13</sup> It has been reported among Buddhists in Sri Lanka<sup>14</sup> and Pakistani Muslim expatriate workers in the Gulf states.<sup>15</sup> It is also widespread in Nepal, Bangladesh, and Pakistan.<sup>8</sup> Immigrants from these countries seen in European and North American clinics<sup>3</sup> do present with this sex-related disorder. The Dhat syndrome has acquired further International recognition by being included in Annex 2 (culture-specific disorders) of the ICD-10 Diagnostic Criteria for Research.<sup>16</sup>

## Clinical Features

Dhat syndrome is usually said to consist of the loss of semen in young men during micturition or while straining to pass stools.<sup>5</sup> Associated symptoms include vague and multiple somatic and psychological complaints such as fatigue, listlessness, loss of appetite, lack of physical strength, poor concentration, and forgetfulness. There may be accompanying anxiety or depressive symptoms. These patients may also present with or without psychosexual dysfunction.<sup>6,12,17</sup> The patient ascribes his symptoms, including sexual dysfunction, to the passage of Dhat (semen or some whitish substance presumed to be semen by the individual) in the urine as a direct result of excessive indulgence in sexual activity or masturbation.<sup>1</sup> Sometimes the sufferer may complain that semen has become foul smelling and less viscous.<sup>4</sup> Apart from a whitish discharge with urine, there are no other urinary symptoms. Urine examination fails to reveal any discoloration, sperms, or any other abnormal constituents except for the occasional oxaluria or phosphaturia.<sup>6</sup> The patient presenting with Dhat syndrome is typically more likely to be recently married, of average or low socioeconomic status (perhaps a student, laborer, or farmer by occupation), comes from a rural

area, and belongs to a family with conservative attitude toward sex.<sup>3,6,18</sup> The most common psychiatric disorders seen in patients with Dhat syndrome include depression, followed by generalized anxiety disorder.<sup>12,19</sup> Presence of concomitant systemic illnesses (resulting in turbidity in urine, e.g., diabetes mellitus, in-born metabolic disorders, urinary tract infections [UTIs], etc.) sexually transmitted diseases (STDs), local genital abnormalities, or drug dependence must be ruled out before labeling Dhat syndrome.<sup>3</sup>

Some researchers<sup>5</sup> have distinguished Dhat syndrome into three subgroups:

- Dhat syndrome alone
- Dhat syndrome with anxiety and depressive symptoms
- Dhat syndrome with sexual dysfunction

It is important to mention that an interview schedule for assessment of Dhat syndrome (DSIS) has already been introduced by research workers<sup>20</sup> at Chandigarh in order to assess this syndrome in the Indian male population.

### Patient's Knowledge, Attitude, and Expectations

Regarding the composition of Dhat, a majority of patients believe that it is semen, followed by those who believe it to be pus, sugar, concentrated urine, infection, or not sure of its composition.<sup>3</sup> Masturbation and/or excessive indulgence in sexual activities, venereal diseases, UTIs, overeating, constipation or worm infestation, disturbed sleep, or genetic factors are believed to be the main etiological factors.<sup>3,18</sup> Majority of these patients get the information about Dhat syndrome from friends, colleagues, or relatives, whereas, some get information from posters, advertisements in mass media, magazines, or quacks. Therefore, these patients prefer to visit STD clinics, urologists, and physicians rather than approach psychiatrists.

### Research on Dhat Syndrome in India

Malhotra and Wig<sup>21</sup> carried out a study to investigate the cultural basis of the Dhat syndrome. They interviewed 107 respondents from the general public. A large segment of the general public from all socioeconomic classes believed that semen loss is harmful. Seminal fluid was considered an elixir of life both in the physical and in the mystical sense, whose preservation guaranteed health, longevity, and super-natural powers. This belief was more frequent in lower socioeconomic classes. The susceptible individual would react to the prevalent belief system and to the fears of semen loss. The symptoms usually disappeared if the misconceptions about semen loss were effectively dealt with. It was expected that with increasing literacy and progress in sex knowledge the syndrome would become less common. Nakra et al.<sup>17</sup> studied 150 male patients presenting with male potency disorders. Of these, 10% had Dhat syndrome alone and another 10.7% had Dhat syndrome along with premature ejaculation or impotency. Compared to patients with sexual dysfunction, patients with Dhat syndrome considered loss of semen as harmful. Behere and Nataraj<sup>18</sup> studied

50 patients with complaints of Dhat syndrome and described the phenomenology of Dhat syndrome. It was most commonly seen in subjects of younger age (16–25 years) and from lower socioeconomic strata. It was commonly associated with impotency, marked anxiety, general weakness, premature ejaculations, and hypochondriasis. Body weakness and hypochondriasis were the commonest complaints. Most of the subjects (88%) were sure that the whitish discharge in urine was semen and majority of them had masturbatory guilt. Singh,<sup>12</sup> in his sample of 50 patients presenting with male potency disorders, reported that 40% fulfilled diagnosis of Dhat syndrome alone and another 22% had Dhat syndrome with impotence. Most of the patients (80%) also had comorbid anxiety and depressive neurosis. Another interesting finding in the study was that about two-third of the subjects did not attend the clinic after initial visit. Authors hypothesized that dissatisfaction with the explanation of disease provided to them could account for such early drop-out from the clinic. In another study from New Delhi, Chadda and Ahuja<sup>6</sup> studied 52 patients presenting with complaint of passage of Dhat in urine. They reported that only 13.5% had diagnosis of pure Dhat syndrome. Most of them had associated psychiatric disorders (neurotic depression–40.4%, anxiety neurosis–36.5%, hypochondriacal neurosis–5.8%, and psychogenic impotence–1.9%). They also reported poor follow-up rates. In another study, Chadda<sup>6</sup> studied illness behavior of 50 Dhat syndrome patients using a Hindi version of Illness Behavior Questionnaire and compared it with that of 50 controls. Two-third of Dhat syndrome patients received unspecified diagnoses on DSM-III-R. Patients with Dhat syndrome showed a distinct illness behavior profile consisting of higher scores on Illness Behavior Questionnaire factors of general hypochondriasis and affective discomfort and lower scores on denial compared with controls, suggesting that the disorder may be a distinct entity. Bhatia and Malik<sup>3</sup> examined 48 consecutive male patients of potency disorders, and reported that about two-third could be classified as Dhat syndrome with or without impotency and/or premature ejaculation; and only 20.8% had impotence alone and 14.6% had premature ejaculation only. The age range of Dhat syndrome patients was found to be 20–38 years (mean 23.5 years) while age of onset was 16–24 years (mean 20.6 years), majority of cases were unmarried (54.2%) and primary educated (79.1%). The cases with Dhat syndrome scored maximally on neuroticism and depression scales. Neurotic depression was the commonest associated psychiatric illness (39.5%), followed by anxiety neurosis (20.8%). The common presenting symptoms of Dhat syndrome included weakness (70.8%), fatigue (68.7%), palpitations (68.7%), and sleeplessness (62.4%), etc. Among the four groups, categorized on the basis of type of treatment (antianxiety drug, antidepressant, placebo, psychotherapy), the best response was seen in those receiving antianxiety or antidepressant drugs while those receiving psychotherapy showed minimal response. The overall dropout rate from treatment was 14.6% and the maximum dropout (40.6%) was seen in psychotherapy group. Bhatia and Malik<sup>3</sup> also reported that 93 of 144 patients with sexual problems complained of Dhat as a major concern. Forty-two percent of cases had diagnosis of Dhat

syndrome only and 23% had Dhat syndrome in combination with sexual dysfunction. In another study, Bhatia<sup>22</sup> studied 60 patients presenting with culture-bound syndromes and reported that Dhat syndrome was the most common culture bound syndrome (76.7%) followed by possession syndrome (13.3%). Depression was the most common associated psychiatric disorder in subjects with Dhat syndrome.

Dhat syndrome has also been described in females. Singh et al.<sup>23</sup> reported a 23-year-old female who attributed her multiple somatic complaints to wetness per vaginum experienced during sexual intercourse. In a study from National Institute of Mental Health and Neuro Science, Bangalore, authors evaluated 31 women who reported “passage of vaginal discharge” and studied the nature and frequency of symptoms considered to have been “caused” by the same. About one-third of the patients who reported passing (nonpathological) vaginal discharge harbored the mis-belief that passage of whitish discharge per vaginum was harmful to their health and that it was causing somatic symptoms in them. The authors considered this description to be akin to Dhat syndrome in men.<sup>24</sup>

## Research from Other Asian Countries

Besides being studied in India, Dhat syndrome has also been reported from and investigated in other South Asian countries. Mumford<sup>25</sup> studied men attending medical clinics in Lahore and reported that about 30% of the subjects complained of Dhat and the prevalence of Dhat was equal in patients with “functional” and “organic” diagnosis. Khan<sup>26</sup> studied the treatment seeking pattern of subjects with Dhat syndrome in Lahore and found that about 50% of the subjects sought help from Hakims; only 1.6% consulted a psychiatrist. In studies from Sri Lanka, De Silva and Dissanayake<sup>14</sup> and Dewaraja and Sasaki<sup>27</sup> studied men with sexual dysfunction and they reported that in many cases the subjects attributed their dysfunction to semen loss. Half of the patients also had somatic symptoms.

## Controversies about the Concept

Many controversies surround the concept of Dhat syndrome. Raguram et al.<sup>28</sup> argued that semen is one of the seven dhatus, hence use of term Dhat is over inclusive and it should be discarded. Authors from various parts of the world have disagreed with the concept of Dhat syndrome as a culture bound syndrome. Mumford<sup>25</sup> argued that “Dhat” should be primarily regarded as a culturally determined symptom associated with depression rather than a separate culture-bound syndrome. Other authors like Sumathipala et al.<sup>29</sup> and Jadhav<sup>30</sup> too reasoned that the symptoms of semen-loss anxiety are reported from various cultures and it should be considered as a culture related rather than culture-bound disorder.

## Management

The management of Dhat syndrome needs serious attention. This syndrome has become the domain of traditional therapeutic

resources, that is, quacks, Ayurvedic or Unani practitioners. The understanding of this condition by modern medicine fails to impress most patients and the explanation and reassurances offered prove not to be of much use. This is further amplified by a study from India, that compared psychological intervention with pharmacological management and not surprisingly found those receiving medications to benefit more at the end of 4 weeks of treatment.<sup>3</sup> Wig<sup>31</sup> too recommended empathic listening, a non-confrontational approach, reassurance, and correction of misbeliefs, along with the use of placebo, anti-anxiety and antidepressant drugs, whatever required.

Avasthi et al.<sup>32</sup> have developed a standardized treatment package for single males presenting with Dhat syndrome. It stresses on sex education and relaxation exercises. Sex education mainly focuses on anatomy and physiology of sexual organs and their functioning with reference to masturbation, semen formation, nocturnal emissions, and their functioning with genitourinary system independent of gastrointestinal tract. Relaxation therapy includes Jacobson's progressive muscular relaxation technique combined with biofeedback (as to facilitate objective evidence and mastering of anxiety by the patient) which should be practiced two to three times/day regularly especially after therapy sessions are over. If there is the presence of associated anxiety or depressive symptoms that may impede the process of therapy, anxiolytics, and/or antidepressants can be added for the least possible duration and in the least possible doses.

Indian Psychiatric Society has formulated clinical practice guidelines for management of various sexual disorders.<sup>33</sup> According to these guidelines, the first step in the management of Dhat syndrome involves evaluation for comorbid sexual dysfunctions, psychiatric disorders, and presence of possible UTI and STDs. Wherever there is a suspicion, local examination, appropriate investigations for infective pathology, and phosphaturia should be done and adequate treatment should be provided. Even after appropriate treatment of these ailments, if the symptoms persist then the subject should be provided with adequate sexual knowledge. Whenever patient has comorbid Dhat syndrome along with premature ejaculation or erectile dysfunction, Dhat syndrome should be treated first. If the psychiatric comorbidity is primary and/or severe, it should be addressed first. According to these guidelines also the most important aspect of treatment of Dhat syndrome is providing adequate sex knowledge and clarifying sexual myths.<sup>33</sup>

## Conclusion

There is sufficient clinical evidence regarding the existence of this culture-bound entity called Dhat syndrome. Due to the contribution of Wig and other researchers, this syndrome was included in the 10th edition of the International Classification of Diseases<sup>34</sup> under other specified neurotic disorders (F 48.8) with the provision of further research.

Apparently, this syndrome has a varied clinical picture. Some have the pure form of the disorder; others have concomitant diagnosable depression and anxiety disorder. Dhat syndrome



may also have comorbid psychosexual dysfunction ranging from concern about potency to frank impotence and premature ejaculation either alone or in combination. However, its phenomenology and prognosis needs to be studied further before this entity is accorded international acceptance.

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# section **XV**

## **MISCELLANEOUS** — *Charlotte A. Gaydos*

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## Introduction

Patients at increased risk for Sexually Transmitted Infections (STIs) are at increased risk for HIV and vice versa due to behavioral, social network, and biological factors.<sup>1-3</sup> Rates of STIs are highest among men who have sex with men (MSM), commercial sex workers, and adolescents.<sup>4</sup> Offering integrated sexual health services in clinics where these high-risk individuals seek care is an efficient strategy to screen, diagnose, treat, and prevent further transmission of STIs and HIV.<sup>5-7</sup> Clinical services for STIs and HIV include the following levels of intervention: prevention, screening, diagnostic testing, treatment, referral for treatment, and partner services. Ideally, to improve efficiency and optimize prevention opportunities in those at risk, these services will be integrated to the greatest extent possible. The range of services offered should be weighed based on the risks of the patient population served, the local epidemiology and the resources available. This chapter outlines the core elements of STI and HIV clinical services in both developed and resource-limited settings.

## Prevention

At a minimum, all patients should be screened with an STI/HIV risk assessment followed by tailored risk reduction counseling. Male and female condoms should be made accessible along with education on appropriate use. If available, pre-exposure vaccination to prevent hepatitis A and B and HPV should be offered to those at-risk who have not previously completed the vaccine series. In the US, Centers for Disease Control and Prevention (CDC) guidelines recommend hepatitis A vaccination for MSM and patients who use illicit drugs (both intravenous drug users [IDUs] and non-IDUs), and hepatitis B vaccination for all unvaccinated, uninfected individuals being evaluated for STIs. HPV vaccination for females age 9–26 years is also recommended.<sup>8</sup> Prevacination serologic screening for hepatitis A and B may save some costs but will also result in missed prevention opportunities due to delay of vaccination initiation in groups who may not return for test results.<sup>8</sup>

Pregnancy testing should be available as a point-of-service test wherever women of child-bearing age seek clinical services with referral to antenatal care or termination services when pregnancy is identified. For prevention of unintended pregnancy, women of child-bearing age attending STI and/or HIV clinics should be screened for pregnancy intentions, contraceptive use and counseled accordingly regarding effective pregnancy prevention. On-site availability of hormonal contraception should be provided if possible and if not, linkage to convenient contraceptive services should be in place. Best practices should include provision of emergency contraception when women who do not wish to become pregnant are evaluated within 5 days of unprotected intercourse.<sup>8</sup>

## Screening and Diagnosis of STIs and HIV

Screening guidelines have traditionally focused on gonorrhea, Chlamydia, syphilis, and HIV. Guidelines for screening of STIs vary by professional organization and take into consideration scientific evidence and expert opinion. Table 107.1 summarizes STI screening recommendations by risk group according to United Kingdom National Screening and Testing guidelines and United States Preventive Service Task Force (USPSTF) guidelines. Specific recommendations for screening and diagnostic tests available for STIs are presented in Chapter 109 and information on screening and treatment for viral hepatitis can be found in Chapter 32.

Table 107.2 shows a summary of UK and CDC guidelines on testing of trichomonas, syphilis and HSV. USPSTF does not provide recommendations on trichomonas testing but recommends serologic screening of syphilis only for patients at increased risk of syphilis infection and HIV screening only for patients at increased risk of HIV infection.<sup>10</sup>

In its recommendations, the USPSTF notes that being at “high risk” or “increased risk” for STIs can include risk irrespective of sexual behavior due to social network and socioeconomic factors that put patients at increased risk. For example, a patient who is in a monogamous relationship in a social network (such as

**Table 107.1:** Summary of United States Preventive Service Task Force and UK Guidelines on Testing of Gonorrhea and Chlamydia among Asymptomatic, Sexually Active Heterosexual Men and Women Attending STI, Adolescent or Family Planning Clinics and MSM based on Site of Possible Infection

	MSM		Women of child-bearing age and heterosexual men seen in STI/adolescent/family planning clinics	
	Asymptomatic	Symptomatic*	Asymptomatic	Symptomatic*
<b>Gonorrhea</b>				
Urogenital	R <sup>†</sup>	R	R <sup>‡</sup>	R
Rectum	R <sup>†</sup>	R	NR	R
Oropharynx	R <sup>†</sup>	R	NR	R
<b>Chlamydia</b>				
Urogenital	R <sup>†</sup>	R	R <sup>§</sup>	R
Rectum	R <sup>†</sup>	R	NR	R
Oropharynx	NR	R	NR	R

\*Refers to UK guideline recommendations only; USPSTF does not provide recommendations regarding testing of symptomatic individuals.

<sup>†</sup>USPSTF guidelines note insufficient evidence for or against screening for gonorrhea or Chlamydia in high-risk men

<sup>‡</sup>USPSTF guidelines recommend screening all high-risk women and all sexually active women regardless of risk <25 years old, report insufficient evidence for or against screening in high-risk men and recommend AGAINST screening in low-risk men and women.

<sup>§</sup>USPSTF guidelines recommend screening all sexually active women <25 years old and all high-risk women ≥25 years old; report insufficient evidence for or against screening asymptomatic men.

Abbreviations: R, recommended; NR, not recommended.

Note: Guidelines for Symptomatic Testing are from UK Guidelines Only.

Adapted from UK guidelines on STI treatment 2006 and USPSTF guidelines on STI screening.<sup>9,10</sup>

**Table 107.2:** Summary of UK and CDC Guidelines on Testing of Trichomonas, Syphilis, HIV and HSV among Asymptomatic and Symptomatic, Sexually Active Heterosexual Men and Women Attending STI, Adolescent or Family Planning Clinics and MSM based on Site of Possible Infection

	MSM		Heterosexual men seen in STI/adolescent clinics		Women of childbearing age seen in STI/adolescent/family planning clinics	
	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic
<b>Trichomonas</b>						
Genital	NR	R <sup>†</sup>	NR	R <sup>†</sup>	NR	R
<b>Syphilis</b>						
Ulcer/skin lesions including condyloma lata	NA	R	NA	R	NA	R
Serum	R	R	R	R	R	R
<b>HIV</b>						
Serum or other approved fluid	R	R	R	R	R	R
<b>HSV</b>						
Ulcer/lesion	NA	R	NA	R	NA	R
Serum	NR	R <sup>†</sup>	NR	R <sup>†</sup>	NR	R <sup>†</sup>

\*Test only if symptoms/signs persist after excluding or treating gonorrhea, Chlamydia and Mycoplasma genitalia infection.

<sup>†</sup>Consider test only if viral detection from ulcer is negative.

Abbreviations: R, recommended; NR, not recommended; NA, not applicable.

Adapted from UK Guidelines on STI treatment 2006 and CDC guidelines.<sup>8,9</sup>

a high school) with a high prevalence of Chlamydia might be at a higher risk of contracting Chlamydia than a patient with high-risk sexual behavior in a social network with a very low prevalence of Chlamydia.

For some STIs, local epidemiology, diagnostic test availability and available resources will influence whether testing and treatment of STIs is offered. In higher resource settings, we recommend at

a minimum offering the diagnostic testing and treatment for symptomatic individuals as described in the above tables. There is some variation for recommended screening of asymptomatic individuals in higher resource settings. Prioritization of screening for these infections in asymptomatic individuals should be based on morbidity associated with infection and prevalence in the communities served. In communities with low rates of return

for test results, point-of-service testing should be used if at all possible. Furthermore, although guidance on gonorrhea and Chlamydia screening may differ somewhat by different professional organizations, it is increasingly common for the testing platform in diagnostic laboratories to perform both tests simultaneously. Therefore, collective specimen testing for both gonorrhea and Chlamydia may be pragmatic, despite modest differences in the utility of screening among groups. Additional diagnostic testing may be indicated in patients with compatible clinical syndrome (i.e., lymphogranuloma venereum testing in MSM with symptoms of proctitis).

## FREQUENCY OF SCREENING

In many cases, there is limited data available to guide the interval for repeat screening. Screening for HIV and for other curable STIs at least once a year is recommended in MSM and sexually active adolescents.<sup>8</sup> More frequent screening (i.e., every 3–6 months) may be warranted in the setting of an epidemic or with very high risk sexual behavior such as multiple and/or anonymous sex partners, illicit drug use with sex, methamphetamine use, and/or sexual partners who engage in these activities.<sup>8</sup> In addition to receiving frequent diagnostic testing services, individuals practicing these behaviors should receive behavioral-based counseling and prevention services. Recommended frequency of asymptomatic screening among HIV-negative heterosexual adolescents and adults depends on the risk behavior of the individual and prevalence of the specific infection in the community.<sup>9</sup> Although annual screening for Chlamydia is a clear guideline for all sexually active young women, ideal frequency of screening in other groups is unknown.<sup>10</sup>

High rates of STIs have been reported among HIV-positive patients<sup>9,11</sup> and there is a well-documented increased risk of HIV transmission with STI coinfection.<sup>1–3,11</sup> Screening for STIs in HIV-positive patients at the time of initial HIV diagnosis should be standard, along with continued testing in continuity care depending upon behavioral risk factors. Annual syphilis serologic testing is recommended in HIV care.<sup>12</sup>

## SCREENING AND DIAGNOSIS OF STIs AND HIV IN PREGNANCY

Untreated STIs can have devastating consequences on pregnancy outcome. Maternal screening for HIV and syphilis as early as possible in the pregnancy allows for opportunities to intervene and prevent transmission to the fetus or infant. The following are summary recommendations for screening of pregnant women for STIs and HIV from the 2010 CDC STD Treatment Guidelines.<sup>8</sup>

### 1. HIV:

- (a) Test as early as possible in pregnancy for HIV.
- (b) Retest women at high risk for HIV in the third trimester (high-risk behavior identified during pregnancy, or linked to sexual networks at risk for HIV).

- (c) Refer all HIV-infected women for highly active antiretroviral therapy in a timely manner.
- (d) Conduct rapid HIV testing in women presenting in labor with undocumented HIV status. If the rapid test is positive, start antiretroviral prophylaxis to women in labor prior to receipt of confirmatory test result to prevent mother-to-child transmission.

### 2. Syphilis:

- (a) Conduct serologic testing for syphilis in the first trimester and/or when pregnancy is confirmed.
- (b) Rescreen women at high risk for syphilis again early in the third trimester and at delivery.
- (c) Screen infants of women whose syphilis status is unknown before discharge to home.
- (d) Screen any woman who delivers a stillborn infant for syphilis.

### 3. Hepatitis B:

- (a) Screen all pregnant women for hepatitis B with hepatitis B surface antigen (HBsAg) in the first trimester even if they have previously been vaccinated or tested.
- (b) Screen/rescreen all women who have not been previously tested for hepatitis B, are at high risk for hepatitis B and/or have clinical hepatitis at the time of admission for delivery.
- (c) Vaccinate all pregnant women at risk for hepatitis B and screen for hepatitis B prior to vaccination.
- (d) Expedited immunoprophylaxis should be given to infants of mothers who test positive for hepatitis B at the time of delivery.

### 4. Chlamydia:

- (a) Test all pregnant women at the first prenatal visit.
- (b) Retest women younger than 25 years and/or at increased risk for acquiring Chlamydia during the third trimester.
- (c) Women diagnosed with Chlamydia in the first trimester should be retested 3–6 months after diagnosis, preferably in the third trimester.

### 5. Gonorrhea:

- (a) Screen all pregnant women at risk for gonorrhea or living in areas with high prevalence of gonorrhea
- (b) Retest women at continued risk in the third trimester.
- (c) Women diagnosed with gonorrhea in the first trimester should be retested 3–6 months after diagnosis, preferably in the third trimester.

### 6. Hepatitis C:

- (a) Screen all women at high risk.

### 7. Bacterial vaginosis:

- (a) Evidence does not support routine screening of asymptomatic pregnant women for bacterial vaginosis (BV).



- (b) All symptomatic pregnant women with BV should be evaluated and treated.

#### 8. Cervical cancer screening

- (a) Screen all women with a Pap test as part of routine prenatal care.

#### 9. *Trichomonas vaginalis*:

- (a) Evidence does not support routine screening of asymptomatic pregnant women for *Trichomonas vaginalis*.
- (b) Symptomatic women should be evaluated and treated appropriately.

#### 10. HSV-2:

- (a) Evidence does not support routine screening for HSV-2 serology in previously undiagnosed pregnant women.

### Treatment/Referral for Treatment

If screening and/or diagnostic testing are offered for STIs, treatment should be made available to the patient by the clinic that provided the test. Whenever possible, point-of-services tests with high sensitivity and specificity should be utilized to decrease time to diagnosis and same-day treatment should be provided as indicated. Presumptive therapy prior to receipt of confirmatory diagnostic test result should be considered depending on the sensitivity of the diagnostic test, likelihood of suspected infection based on clinical presentation and local epidemiology, likelihood that the patient will return to receive test results and potential morbidity related to untreated infection.

For clinics that do not have expertise in HIV treatment services, patients diagnosed with HIV should be given timely referral to clinics that provide HIV treatment. A follow-up mechanism should be in place to ensure linkage to HIV care.

### HIV CLINICAL SERVICES

Core components of HIV clinical services include clinical evaluation and staging of HIV infection by a clinician trained in HIV care, routine laboratory evaluation with CD4 and HIV viral load, prescription of antiretroviral therapy and opportunistic infection prophylaxis when indicated, treatment-adherence counseling, and risk-reduction counseling. Risk-reduction counseling includes pre-conception counseling, discussion of risky sexual and drug use behaviors as well as counseling of HIV discordant couples (preferably together). STI and family-planning services should also be included in HIV clinical care both for the health of the HIV-positive patients receiving services and to decrease transmission to others. See Chapter 115 for guidelines on treatment of HIV in industrialized and resource-limited settings.

### Screening and Treatment of STIs in Resource-Limited Settings

Efficient allocation of resources to address STIs and HIV is a priority in all clinical venues but is of particular concern in resource-limited settings. The greatest share of the global burden of STIs and HIV occur in these countries where availability of treatment is often limited and diagnostic testing is often unavailable and/or unreliable.<sup>13</sup> To efficiently diagnose, treat and decrease transmission of STIs in asymptomatic individuals, the WHO recommends syndromic management with targeted diagnostic screening to high-risk individuals, integration of STI and HIV screening in family planning clinics, and enhanced partner services including expedited partner therapy.<sup>7</sup> In syndromic management, STI-associated syndromes are recognized and empirically treated with medications that target the most common causes of the specific syndromes without the use of diagnostic tests.<sup>7,14</sup> Algorithms for management are developed based on the local prevalence and the antimicrobial susceptibility of the most likely etiologies of the syndromes. Syndromic case management has generally been shown to be cost-effective in many low-resource settings, particularly when applied to clinical scenarios in males and with genital ulcer syndromes. Reports indicate that the syndromic approach to cervicitis in women has less utility, and refining approaches here may be an area for productive clinical research.<sup>14</sup> For more information on syndromic management of STIs, see also Chapters 56, 60, and 61.

### Partner Services

In order to break the chain of STI transmission to the wider community, sexual partners of patients with STIs must be treated. Ideally, partner-management services can be integrated into the clinic in which the index receives care. Through partner services, sexual contacts of patients diagnosed with STI(s) are informed of their exposure, offered evaluation and presumptive treatment for infection, and counseled on prevention of future infection.<sup>5</sup> Partners can be notified through the index patient and/or with the assistance of the local health department with level of partner notification services available varying by STI prevalence and resources available. Through partner notification and treatment, index patients are at decreased risk for reinfection and at a population level, rates of forward transmission are inferred to be decreased.<sup>8</sup>

In resource-limited settings and in situations where partners are unable or unwilling to come to clinics for evaluation and treatment, expedited partner therapy (EPT) may be considered. In this intervention, partners of infected patients are treated through medications or prescriptions without medical evaluation or prevention counseling. Compared to standard partner services, EPT has been shown to increase likelihood of partner treatment and decrease exposures to untreated partners compared to unassisted patient referral. EPT also leads to decreased risk of reinfection with gonorrhea or Chlamydia compared to standard partner services.<sup>15</sup> For more details on partner services and EPT see Chapter 17.

### Summary

Through integrated STI, HIV and family planning services, individuals with high-risk sexual behavior are targeted for screening, diagnosis, and treatment of STIs and unintended pregnancy. The services clinics provide will depend on the patient population served, burden of disease, local epidemiology, and resources available. Guidelines for screening and treatment are available and should be tailored to meet the needs of the communities served. With this approach, reduction of the significant individual and public health costs associated with STIs and HIV can be achieved.

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# Medicolegal Aspects of Sexually Transmitted Infections and Sexual Assault

Margaret R. Hammerschlag

108

## Sexually Transmitted Infections and Sexual Assault in Children

Testing for sexually transmitted infections (STIs) in children presents a number of problems for the practitioner that are not usually faced when testing adults for the same infections. The identification of an STI in a child can have serious legal in addition to medical implications. The presence of an STI is often used to support the presence or allegations of sexual abuse and conversely, the identification of an STI in a child will prompt an investigation of possible abuse. Although the identification of sexually transmissible agents in children beyond the neonatal period suggests sexual abuse, exceptions do occur. Perinatally acquired rectal or vaginal *Chlamydia trachomatis* infection may persist for 2–3 years after birth.<sup>1</sup> Genital warts have been diagnosed in children who have been sexually abused, but also in children who have no other evidence of sexual abuse.<sup>2–5</sup> Bacterial vaginosis (BV) has been diagnosed in children who have been abused, but its presence alone does not prove sexual abuse.<sup>6</sup> However, postnatally acquired gonorrhea; syphilis; and nontransfusion, nonperinatally acquired HIV are virtually diagnostic of sexual abuse.<sup>7</sup>

## Epidemiology of STIs in Children being Evaluated for Suspected Sexual Abuse

Studies of STIs in children have demonstrated significant variability in the prevalence of infection. In many of the earlier studies, only symptomatic children were tested, which often gave higher prevalence of gonococcal infection than studies that tested all children being evaluated for suspected sexual abuse. However, the prevalence of STIs in sexually abused children is low, usually 3% or less.<sup>8–12</sup> The results of four recent studies examining the epidemiology of STIs in children and adolescents being evaluated for suspected sexual abuse are summarized in Table 108.1. Three studies were retrospective chart reviews, including one each from Vienna, Austria<sup>8</sup>; Auckland, New Zealand<sup>9</sup>; and Miami, Florida.<sup>10</sup> Charts were examined from a total of 4350 children, who were seen over periods ranging from 4 to 7 years. The ages ranged from 0 to 17 years and the overwhelming majority was female. Despite differences in population and methodologies, the results of these studies were fairly consistent. The prevalence of STIs, specifically gonorrhea and *C. trachomatis*, was low, ranging from 0.4% to 1.8%. No child was found to have syphilis or

**Table 108.1:** Selected Studies of Prevalence of Sexually Transmitted Infections (STIs) in Children Being Evaluated for Sexual Abuse

Study (ref)	N positive/tested (%)							
	N (total)/ % Female	<i>N. gonorrhoeae</i>	<i>C. trachomatis</i>	Syphilis	HSV	<i>T. vaginalis</i>	HPV	HIV
Giradet et al. <sup>12*</sup>	536 (90.5)	16/483 <sup>†</sup> (3.3)	15/482 (3.1)	1/384 (0.3)	5/12 (42) <sup>‡</sup>	5/85 (5.9)	NS	0/384
Kelly & Koh <sup>9†</sup>	2162 (85.8)	11/1690 (0.7)	20/1668 (1.2)	0/838	8 <sup>□</sup>	6/1288 (0.5)	67/2162 (3.1)	0/301
Kohlberger et al. <sup>8†</sup>	180 (100)	1/56 (1.8)	1/62 (1.6)	0/5	NS <sup>§</sup>	1/136 (0.7)	NS	0/27
Simmons & Hicks <sup>10†</sup>	2763 (100)	10/2007 (0.5)	10/2007 (0.5)	ND <sup>‡</sup>	ND	ND	ND	ND

\*Prospective study.

†Retrospective chart review.

‡ND: not done.

§NS: not specified.

□Number of children tested not stated.

‡Denominator females, none of the males were positive for any STI.

#Testing only done in children with lesions suggestive of HSV.



HIV by serology. As these were retrospective chart reviews they had a number of major limitations. There were different inclusion criteria and not every child or adolescent was tested for every STI. Giradet et al.<sup>12</sup> prospectively examined children 0–13 years of age being evaluated for suspected sexual abuse/assault at 7 tertiary care centers in the United States (Houston, TX; Atlanta, GA; Harrisburg, PA; and New York City, NY). All children were tested at multiple sites for *N. gonorrhoeae* and *C. trachomatis* by culture and vaginal and urethral swabs and urine were also tested using two nucleic acid amplification tests (NAATs). Wet mounts were performed for *T. vaginalis* and cultures for herpes simplex virus (HSV) were done if lesions were present. Sera were also obtained for testing for syphilis, HIV, and type specific antibody for HSV-1 and 2. A total of 536 children were enrolled, 485 (90.5%) were female. None of the 51 boys enrolled were positive for any STI. Overall, 40 (8.2%) of the girls were found to have one or more STIs. *C. trachomatis* and *N. gonorrhoeae* were detected by culture and/or NAAT in 15 (3.1%) and 16 (3.3%) of the girls enrolled, respectively. *T. vaginalis* was detected by wet mount in 5 of 85 (5.9%) symptomatic girls tested. Serologic evidence of syphilis was found in only one of 384 (0.3%) children. This child also was positive for *N. gonorrhoeae*. None of the children were positive for HIV. Cultures for HSV were obtained from only 12 children who had lesions suggestive for HSV, 5 (41.7%) were positive, but only 1 of the culture positive children had type specific HSV-2 antibody. Although girls who presented with vaginal discharge were more likely to have a positive test result (24.5% vs 6.3%), 67.5% of the children with a confirmed STI had normal or nonspecific anogenital findings. The overall prevalence of STIs varied from site to site, ranging from 1.7% in Texas to 7.8% in Atlanta.

## Diagnosis of STIs in Children

As the prevalence of STIs in children is low, the positive predictive value of a test is more important than in an adult victim of assault. One needs to use tests with the highest specificity. One cannot extrapolate the performance of a test in adults to children.

### NEISSERIA GONORRHOEAE

The identification of *N. gonorrhoeae* in a child beyond the neonatal period is indicative of some kind of sexual contact. The Centers for Disease Control and Prevention (CDC) 2006 STD Treatment Guidelines recommends that specimens for culture of *N. gonorrhoeae* be collected from the pharynx and anus of girls and boys, the vagina in girls, and the urethra in boys being evaluated for suspected sexual abuse.<sup>7</sup> The Guidelines also specifically stated that Gram-stained smears not be used for the diagnosis of gonorrhea in children. The 2010 Guidelines now include recommendations for the use of NAATs for detection of *N. gonorrhoeae* in children.<sup>13</sup> Use of NAATs has supplanted standard culture methods for *N. gonorrhoeae* in many laboratories. All the currently available assays have approval from the US Food

and Drug Administration (FDA) for use in genital sites (cervix, vagina, urethra) and urine from adolescents and adults. None are approved for extragenital sites in adults (pharynx or rectum) or for any site in children.

To date, there have been three published studies that compared NAATs to *N. gonorrhoeae* culture in children being evaluated for suspected sexual abuse.<sup>14–16</sup> All included urine specimens as well as vaginal swabs. Although the results of the two earlier studies suggested that the sensitivity of NAATs for *N. gonorrhoeae* was similar to culture, they both had several serious limitations: the populations studied were predominantly female and included adolescents up to 18 and 20 years of age many of whom reported consensual sexual activity, only 23.7% and 41.5% of the children enrolled were prepubertal<sup>14,15</sup> and both studies utilized ligase chain reaction (LCR, LCx, Abbot Diagnostics), which was taken off the market in 2002 because specificity concerns for detection of *N. gonorrhoeae*.<sup>17</sup> Other study limitations included the failure to use an independent reference standard in estimating test performance, failure to separately analyze test performance by age and gender (when applicable). The prevalence of *N. gonorrhoeae* infection in both studies was low (1.9% and 3.2%) reducing the precision of sensitivity estimates. The number of extragenital specimens was also too low to assess test performance at those sites. Black et al. recently evaluated the use of strand displacement amplification (SDA) and transcription mediated amplification (TMA) vs. culture for diagnosis of *N. gonorrhoeae* in children, 0–13 years of age, evaluated for sexual abuse in four US cities.<sup>16</sup> All children were tested at multiple sites for *N. gonorrhoeae* and *C. trachomatis* by culture and vaginal and urethral swabs were tested with SDA and urine with SDA and TMA. Positive NAATs for *N. gonorrhoeae* were confirmed by an in-house PCR using an alternate target, the *Hinf*I fragment of the 4.2-Kb cryptic plasmid.<sup>18</sup> A total of 536 children were enrolled, none of the 51 boys were positive for *N. gonorrhoeae* by any test at any site. Of the 485 female participants, 16 (3.3%) had a positive result for *N. gonorrhoeae* by any test: 12 (2.5%) by culture, 14 (2.9%) by vaginal NAAT, and 14 (2.9%) by urine NAAT. All participants who had a positive vaginal culture for *N. gonorrhoeae* had positive urine NAATs. There were discrepant results in two cases (both SDA-positive and TMA-negative). One of these girls was positive in urine and negative by vaginal swab, the other was positive both by urine and swab. All SDA-positive results for *N. gonorrhoeae* were confirmed to be true positives by a species-specific *N. gonorrhoeae* PCR. Three girls had discrepant results by site: two were vaginal swab positive and urine negative, one was vaginal swab negative and urine positive. The results of this study suggest that SDA and TMA may be alternatives to culture for the detection of *N. gonorrhoeae* in vaginal swabs and urine in prepubertal girls.

Not all NAATs perform equivalently. PCR and SDA have both been demonstrated to have cross reactivity with other *Neisseria* species including *N. cinerea*, *N. flavescens*, *N. lactamica*, *N. sicca*, and *N. subflava*.<sup>19–21</sup> This can have important implications especially when testing extragenital sites, especially the pharynx.

Although false-positive results were not observed with SDA in the multicenter study,<sup>16</sup> it still remains a possibility, especially if the assay is used more widely. Additional testing is still essential as the prevalence of gonorrhea in children being evaluated for suspected sexual abuse is low; low positive predictive values have been reported in low-prevalence adult populations.<sup>22</sup> One cannot extrapolate from these results to other NAATs, specifically PCR, or use in extragenital specimens (pharynx, rectum) or in any site in boys.

## CHLAMYDIA TRACHOMATIS

The prevalence of *C. trachomatis* infection in abused children is also low (Table 108.2). Genital infection with *C. trachomatis* in children is frequently asymptomatic and may persist for months to years.<sup>23</sup> The 2006 CDC Guidelines recommended that children being evaluated for suspected sexual abuse be tested for *C. trachomatis* at the anus in both boys and girls and from the vagina in girls.<sup>7</sup> Culture was the preferred test. Pharyngeal specimens from children of either sex are also not recommended, as the prevalence of *C. trachomatis* infection at this site is very low in children being evaluated for suspected sexual abuse. The isolation of *C. trachomatis* in tissue culture should be confirmed by the microscopic identification of the characteristic intracytoplasmic inclusions, preferably with a species-specific fluorescein-conjugated monoclonal antibody.<sup>7</sup> Use of genus-specific antibody for culture confirmation can lead to misidentification of *C. pneumoniae* as *C. trachomatis* in pharyngeal specimens.<sup>24</sup> Enzyme immunoassays (EIAs) are not acceptable as confirmatory tests and have been associated with false positive results, especially when used with vaginal and rectal specimens.<sup>25–28</sup>

NAATs are currently approved by the FDA for detection of *C. trachomatis* from genital sites (cervix, vagina, urethra) and urine from adolescents and adults. None are approved for extragenital sites (pharynx or rectum) in adults or have approval for any site in children. These methods have been found to have excellent sensitivity for detection of *C. trachomatis*, usually well above 90%, in genital specimens and urine from adult men and women, while maintaining high specificity.<sup>29</sup> The 2006 STD Treatment Guidelines recommended that NAATs can be used in children being evaluated for suspected sexual abuse if culture is not available and if positive results can be confirmed.<sup>30</sup> Confirmation was specified as use of another NAAT that utilized a different genetic target, however, not all NAATs perform equally.<sup>29</sup> Use in extragenital specimens was not discussed. As with *N. gonorrhoeae*, data on the use of available NAATs for detection of *C. trachomatis* in children are limited. The number of studies is small and have the same limitations described previously for evaluation of NAATs for *N. gonorrhoeae*.<sup>14,15,30</sup> The recent multicenter study by Black et al.,<sup>16</sup> also evaluated the use of SDA and TMA with urine and genital swabs (vagina and urethra) compared to culture for diagnosis of *C. trachomatis* in children. All samples were processed and tested according to manufacturers' protocols except for the TMA tests which were performed on previously frozen urine or swabs collected in the BD ProbeTec sample collection medium. Test results that were positive by SDA for *C. trachomatis* were confirmed using an in-house PCR targeting the *ompA* gene, performed at the CDC.<sup>31</sup> Fifteen (3.1%) of 485 female participants had a positive result for *C. trachomatis* by any test (1.4% by culture; 2.3% by vaginal NAAT; 2.7% by urine NAAT). None of the male participants had any positive

**Table 108.2:** Recommended Tests for STIs in Children Being Evaluated for Suspected Sexual Abuse

Infection	Reportable as sexual abuse	Sites and specimens	Recommended tests
<i>N. gonorrhoeae</i>	Diagnostic	Vagina, urethra (males), rectum, pharynx, urine (if NAAT is used)	Culture on selective media, isolates confirmed by at least 2 methods that use different principles. NAATs <sup>†</sup> in vaginal swab or urine from girls. NAATs not approved for pharynx or rectum
<i>C. trachomatis</i>	Diagnostic <sup>*</sup>	Vagina, urethra (males), rectum, urine (if NAAT is used)	Culture: tissue culture, confirmation by staining with FA conjugated species-specific monoclonal antibody with visualization of characteristic intracytoplasmic inclusions. NAATs <sup>†</sup> may be used if culture is not available and results can be confirmed by a second NAAT. NAATs not approved for rectal specimens.
Syphilis	Diagnostic <sup>*</sup>	Serum, active lesions	Serology: initial screening with nontreponemal test, confirmation with treponemal test. Darkfield microscopy to identify treponemes in lesions
HSV	Suspicious	Lesions on vagina, urethra (males), rectum	Culture. Screening using type-specific serology not recommended
<i>T. vaginalis</i>	Highly suspicious	Vagina	Examination of vaginal wet mount. Culture
HPV	Suspicious	Vagina, urethra (males), rectum	Physical examination. Biopsy and HPV typing of lesions
HIV	Diagnostic <sup>*</sup>	Serum	EIA, followed by WB, viral load

\* If perinatal acquisition can be ruled out.

<sup>†</sup> Data on use of NAATs in children limited to SDA and TMA, vagina and urine in females.

cultures or NAATs for *C. trachomatis*. All participants who had a positive vaginal culture for *C. trachomatis* also had positive urine NAAT. Two girls had positive *C. trachomatis* cultures from rectal swab specimens, but negative vaginal swab specimens by both culture and NAATs, and negative urine NAATs. There were no discrepant results in any of the participants tested by SDA and TMA for *C. trachomatis*. All *C. trachomatis*-positive results were confirmed by DNA sequence genotyping. The sensitivity of vaginal culture for *C. trachomatis* was 39% in all girls studied. In contrast, the sensitivities of urine and vaginal swab NAATs were 100% and 85% in all female children, respectively, for detection of *C. trachomatis*. The results of Black et al.<sup>9</sup> suggest that NAATs can be used for detection of *C. trachomatis* in girls being evaluated for suspected sexual abuse. However, the same limitations apply as for use of these assays for detection of *N. gonorrhoeae*: (i) As the prevalence of *C. trachomatis* in this population is low, additional testing is probably necessary. (ii) One cannot extrapolate from these results to other NAATs, specifically PCR and use in specimens other than vagina and urine in girls. (iii) One cannot make any recommendations on the use of these assays in prepubertal boys. Some of the more recently available commercial NAATs, such as TMA (Aptima 2), offer an alternate target confirmation method that can be used on the same testing platform; however, there are no data on the use of this confirmatory test in this setting. Additional options include sending blinded specimens to an independent or reference laboratory for confirmation testing, confirming a NAAT-positive result by culture test (requires a separate, invasive specimen), or use of a second, alternate technology commercial NAAT. Specimens collected from children for forensic applications should be retained in the laboratory for purposes of additional testing, in accordance with local policies and procedures.

## SYPHILIS

The prevalence of syphilis in these children has been <1% in most studies.<sup>8–12</sup> Diagnosis of syphilis was based on serologic screening as most of these children were asymptomatic. Cases of symptomatic syphilis appear to be uncommon and are mostly limited to anecdotal reports. Clinical findings have included primary chancres, manifestations of secondary syphilis including rash and condyloma lata, which can be misdiagnosed as genital warts.<sup>32</sup> The major confounding variable in the diagnosis of syphilis in children beyond the neonatal period is differentiating between acquired and congenital infection. As most pregnant women in the US are screened for syphilis during pregnancy, congenital infection could be ruled out if maternal records can be accessed. However, this may not always be possible and some of the clinical manifestations of congenital syphilis may overlap with those of acquired syphilis.

## HERPES SIMPLEX VIRUS

The presence of genital herpes in a prepubertal child also raises the probability of sexual abuse. However, available data are too limited

to allow estimation of the likelihood of sexual transmission. The overwhelming majority of published studies of STIs in children being evaluated for sexual abuse have limited studies for HSV to children who presented with suggestive genital lesions. The prevalence of HSV infection in these studies was low, <5%.<sup>8–12</sup> In the multicenter study reported by Giradet et al., only 12 girls were found to have genital ulcers, and only five were culture positive for HSV.<sup>12</sup> As most studies have only tested symptomatic children, we have no way of knowing how common asymptomatic infection may be in these children, even as more evidence emerges about the frequency of asymptomatic and subclinical infections in adults.

Data on use of type specific serology for HSV-1 and 2 in children are very limited. Ramos et al., compared HerpeSelect HSV-2, Biokit HSV-2 Rapid Test (Biokit), and western blot (WB) in sera from 150 children being seen in a sexual abuse clinic.<sup>33</sup> The ages ranged from 1 to 18 years and 81% were female. Fifty-one percent of the children were HSV-1 seropositive by WB. In contrast, <1% were seropositive for HSV-2. Although 8 patients were positive for HSV-2 by at least one test, only one individual was positive by all three tests, an adolescent girl who reported consensual sexual activity. Six children were positive by HerpeSelect HSV-2, but negative by Biokit and WB and 137 samples were consistently negative. None of the children had clinical genital herpes. Sera from 283 children enrolled by Giradet et al.<sup>12</sup> were tested for HSV-1 and 2 antibodies using an immunodot enzyme assay with a monoclonal antibody inhibition for confirmation performed at the CDC. Antibody to HSV-1 and HSV-2 was detected in 45.6% and 2.5% of the children, respectively. Three children had antibody to both HSV-1 and 2. As stated previously, cultures for HSV were obtained from only 12 children who had lesions suggestive of herpes, but only one of five culture positive children had HSV-2 antibody. These data suggest that type-specific serology for HSV has a poor predictive value for diagnosis of HSV infection in children being evaluated for suspected child abuse, based on a single serum sample. Furthermore, as demonstrated by Ramos et al.,<sup>33</sup> the performance of even FDA approved tests can be inconsistent in a low prevalence population.

## TRICHOMONAS VAGINALIS

Although *T. vaginalis* is probably the most prevalent nonviral STI among adults in the US, data on this infection in the setting of child sexual abuse are limited. Most published studies of STIs in sexually abused children have testing for *T. vaginalis* was limited to girls presenting with vaginal discharge.<sup>8–12</sup> Rarely *T. vaginalis* can be transmitted vertically from mother to infant (vaginal, urine) during parturition.<sup>34</sup> These infections may persist for several months after birth. Care should be taken in interpretation when trichomonads are reported present in urine specimens from children collected for another purpose. As the morphology of *Pentatrichomonas (Trichomonas) hominis*, a nonpathogenic intestinal flagellate, is very similar to that of *T. vaginalis*; care must be taken to make sure that specimens are not contaminated with fecal material which can occur with bagged urine specimens.



Culture for *T. vaginalis* on Diamond's medium has a high sensitivity (95%) and specificity (>95%) in adult women.<sup>35</sup> Incubation periods of 2–7 days are needed to identify *T. vaginalis* in culture.<sup>35</sup> There are several point of care tests available including the Affirm VP III Microbial Identification System (Becton Dickinson) test, which is a direct nucleic acid probe hybridization test for detection of *T. vaginalis*, *Gardnerella vaginalis*, and *Candida spp.*<sup>36,37</sup> It has been reported to have sensitivities of 80–90% in adult women with vaginitis.<sup>36</sup> The Affirm VP III has not been validated or approved for use in genital specimens from prepubertal girls or urethral specimens from men.

## HUMAN PAPILLOMAVIRUS (HPV)

The association of genital warts and sexual abuse in children is complicated by the long period of latency before lesions become clinically apparent and possibility of nonsexual transmission, either vertically during delivery or horizontally after birth. The criteria for diagnosis of HPV infection in children, clinical versus detection of HPV DNA, are also not standardized. Most published studies of HPV infection in children being evaluated for sexual abuse have relied on the presence of clinical lesions consistent with genital warts for the diagnosis of HPV infection.<sup>2,8–12</sup> Given the possible role of perinatal transmission for anogenital and respiratory HPV (laryngeal papillomatosis) infection, an important issue has been at what age is the presence of HPV infection due to sexual abuse. Although studies and reviews of the subject have suggested that 24 months of age was the upper limit for anogenital warts in children to be secondary to perinatal transmission, a significantly longer incubation period,  $\geq 5$  years, has been suggested for laryngeal papillomatosis.<sup>4</sup>

The diagnosis of HPV infection in children has been primarily clinical. Lesions suspicious for HPV should be biopsied and tested for HPV. Several studies have evaluated detection of HPV DNA in children being evaluated for suspected sexual abuse, however the results have been contradictory.<sup>2–5,38</sup> Studies published since 2000 have demonstrated poor correlation of detection of HPV DNA by PCR and presence of genital warts.<sup>3–5</sup> There is also a great deal of heterogeneity of the PCR methods used. Due to the large number of HPV types involved in genital disease, type-specific PCR assays are not practical for detection of HPV. Most have used generic primers followed by either probing or sequencing of the products. Nested-PCR assays were used in some studies. Use of generic HPV PCRs may be less sensitive than specific HPV 16 PCR. Even so, the association of the presence of HPV DNA with abuse is not very strong. HPV DNA has been detected in genital and rectal swabs in 15% of girls thought to be abused, and it has also been detected in vaginal and/or anal specimens from 2.1% of healthy children with no history of abuse.<sup>3–5,38,39</sup>

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# Sexually Transmitted Infections: Screening and Diagnostic Practices

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# 109

## Introduction

Sexually transmitted infections (STIs) are of utmost importance because of their cosequential diseases/complications. These are especially concerning in women, who can experience cervicitis, endometritis, pelvic inflammatory disease (PID), chronic pelvic pain, adverse birth outcomes, and infertility. In men, gonorrhea and chlamydia infections cause urethritis, epididymitis, and proctitis. Ulcerative diseases such as syphilis, lymphogranuloma venereum (LGV), chancroid, and herpes simplex virus (HSV) can cause systemic illness. Long-term adverse health events include the sequelae of untreated STIs, such as chronic pelvic pain, tubal infertility, vertical transmission to neonates, and for both men and women increased risk of HIV transmission and acquisition.<sup>1</sup>

Sexually transmitted infections disproportionately impact individuals with various demographic and behavioral risk factors, or persons who live in defined geographic areas. The prevalence of STIs is higher among young adults aged 15–24 years, urban dwellers, and individuals with high-risk sexual behavior, such as multiple partners or exchanging sex for money or drugs.<sup>2</sup>

## Rationale for Screening Practices

Many if not most STIs are asymptomatic; thus, screening of individuals is highly recommended. Screening can be defined as performing tests for STIs among individuals who do not have symptoms of an STI and who are not presenting to a clinician because of symptoms or being a named contact of a person who is infected, where “diagnostic” testing may be performed. The World Health Organization (WHO) recommends assessment and testing for syphilis, gonorrhea, chlamydia, trichomoniasis, genital ulcer disease, and urethral discharge in settings where patients are seen, and also in settings without relation to symptoms, including detention facilities, military recruitment, routine sex worker examinations, and women at delivery.<sup>2</sup> The primary goals of STI assessment and monitoring are to identify population subgroups with a high prevalence of disease, to monitor trends in STI prevalence, and to prevent transmission and morbidity due to asymptomatic infection.<sup>2</sup> Limited financial

and personnel resources have led to the development of selective screening criteria in some areas in order to maximize identification of infected persons when resources are limited which limit the number of persons screened.

Asymptomatic infection or mild symptoms can lead to delay in diagnosis and treatment.<sup>3</sup> Syndromic diagnosis will not work to detect individuals with asymptomatic or unrecognized infection; such persons are an important reservoir for continued transmission to partners. Thus, the importance of regular screening among high risk populations must be adopted rather than syndromic treatment, which has been the WHO standard of care. The syndromic management approach has low sensitivity and low positive predictive value.<sup>2</sup> Selective screening is often instituted because of resource constraints, but requires a local prevalence study first to identify those at risk in a particular population. Numerous studies have shown that screening for STIs, based on age, behavioral, and clinical characteristics, or in some instances universally, effectively prevents the costly consequences of disease progression.<sup>4–7</sup> Selective screening algorithms, based on demographic and behavioral risks, have been explored in a variety of situations in an attempt to maintain efficient use of resources. This chapter discusses STI screening strategies and new sample types that are aimed at maximally preventing morbidity and transmission. Age has been determined to be an excellent predictor of risk for chlamydia infections. Both <25 and <30 have been found to be useful in large screening programs.<sup>4,8,9</sup> Studies have also shown that individuals who practice high risk sexual behaviors, such as new or multiple sex partners or who do not use condoms, are at greater risk for chlamydia infections.<sup>8,10</sup>

## Screening for Sexually Transmitted Infections to Prevent Morbidity and Sequelae

### CHLAMYDIA TRACHOMATIS AND NEISSERIA GONORRHOEA

Screening interventions for chlamydia and gonorrhea in women in developed countries are cost-effective because of the estimated savings in prevented future consequences of PID and infertility. It is estimated that 10–25% of women with untreated chlamydia



and gonorrhea will experience PID, 20% of women with PID will have tubal infertility, and 9% will have ectopic pregnancies.<sup>4,5,11</sup> A study of fertility among 1844 women with abnormal laparoscopy and suspected PID found 10.8% had a confirmed tubal factor infertility, and 9.1% ectopic pregnancy rate, compared to 0% and 1.4%, respectively, among 657 women with normal laparoscopic findings.<sup>12</sup> Ectopic pregnancy, tubal infertility, chronic pelvic pain, and other long-term consequences of PID, such as ectopic pregnancy, are estimated to occur among 15% to 20% of women with PID.<sup>12,13</sup>

A large proportion of chlamydia and gonorrhea infections, in both men and women are asymptomatic, with percentages ranging from 30% to 50% in men, and 60–80% in women.<sup>11,14</sup> In women especially, symptoms are variable and can be nonspecific, leading to delay in diagnosis and treatment seeking.<sup>3,12</sup> A randomized, controlled trial evaluating an enhanced screening intervention for chlamydia found a reduced incidence of PID among women who received screening compared to those who sought care based on symptoms.<sup>15</sup> Early detection and treatment with subsequent prevention of long-term health consequences and vertical transmission is facilitated by screening among asymptomatic individuals. However, screening in many settings is hampered by the relative lack of clinical facilities and by the cost of the tests themselves.

### Diagnostic Methods—Chlamydia

Historically, chlamydiae were cultivated in tissue culture, but cell culture has been replaced by nonculture assays. Culture for detection of chlamydiae in clinical specimens is generally now only performed at reference laboratories. The first nonculture assays, such as Direct Fluorescent Antibody (DFA) staining of direct patient material and enzyme immunoassay, have been replaced by molecular tests which can amplify the nucleic acids in clinical specimens are currently the tests of choice and several are available commercially.<sup>16–19</sup> These nucleic acid amplification tests (NAATs) are currently recommended by Centers for Disease Control and Prevention (CDC) as the diagnostic assay of choice.<sup>20</sup> Inexpensive, point-of-care tests (POC), which can be used by minimally trained healthcare workers, are desperately needed. Such tests could eliminate the need for clinical facilities and could be used in community settings.<sup>21</sup>

### Diagnostic Methods—Gonorrhea

The gram stain and culture on specialized laboratory media with biochemical confirmatory assays has been used for many years to detect *N. gonorrhoeae* in clinical specimens.<sup>22</sup> Urethral smears from males with symptomatic gonorrhea have a sensitivity of 90–95.0%.<sup>23</sup> Endocervical smears from females and rectal specimens require careful interpretation, because of colonization with other gram-negative coccobacillary organisms and in females the sensitivity of an endocervical Gram-stain is estimated to be 50–70.0%.<sup>23</sup> Presently, the nucleic acid-based tests (NAATs) are the most sensitive assays available and are currently recommended by the CDC.<sup>20</sup>

### Choice of Specimen Type for Screening

For chlamydia and gonorrhea, the samples traditionally used have been cervical swabs for females and urethral swabs for males. However, due to the extreme increase in sensitivity and specificity of NAAT assays, less invasive samples such as urine for both females and males, as well as vaginal swabs for females, can be also used. Centers for Disease Control (CDC) now recommends that for screening of asymptomatic women the self-collected vaginal swabs should be used, since they are slightly more sensitive than urine.<sup>20</sup> However, urine screening tests are often used in outreach screening programs.

When pelvic examinations are being performed for symptoms or because a Pap test is required, the cervical swab is usually preferred as this sample type has been shown to have a slightly higher organism load for chlamydia.<sup>24</sup> However, if an individual is not receiving a pelvic examination, clinicians should take advantage of the ease of obtaining a urine sample or a self-collected vaginal swab for amplification testing for chlamydia and gonorrhea. Vaginal swabs are therefore the preferred sample type for screening; as well, they are highly preferred by many women.<sup>25–33</sup> Such samples can eliminate the necessity for a clinician-performed pelvic examination for asymptomatic women for sample collection and may be cost savings, when a Pap test is not required.<sup>34</sup> For males, urine specimen is the sample of choice for the detection of chlamydia.<sup>35,36</sup> Infections detected by NAATs may be up to 80% higher than those found with the use of older technology.<sup>37</sup>

The resulting expansion of screening programs for chlamydia and gonorrhea has resulted in recommendations by professional organizations and public health officials in the United States to screen all sexually active women <26 years yearly or those >26 years with sexual risk factors.<sup>38,39</sup> No official recommendations exist for men but CDC guidance has been published.<sup>40</sup>

### Alternative Specimen Types

Rectal and pharyngeal specimens are important sample types for detection of chlamydia and gonorrhea in men who have sex with men (MSM). Such sample types are not cleared by the FDA, but have been extensively demonstrated by many research studies to perform well with NAATs assays and yield better results than culture.<sup>41,42</sup> However, specimens from rectal and pharyngeal sites require verification of test performance by individual laboratories before use. Eye samples from babies or ocular samples from adults can be tested by NAATs, but since FDA clearance has never been obtained for commercial tests, laboratories must perform their own verification studies. NAATs are also becoming increasingly used for diagnostic assays for cases of sexual abuse.<sup>43</sup>

### Diagnostic Considerations and Assay Choice

Because NAATs measure nucleic acids instead of live organisms, caution should be used in using NAATs for test-of-cure assays. Residual nucleic acid from cells rendered noninfective by antibiotics may still give a positive amplified test up till 3 weeks after

therapy, when the patient is actually cured of viable organisms.<sup>44,45</sup> Therefore, clinicians should not use NAATs for test-of-cure until after 3 weeks. The CDC currently does not recommend a test-of-cure after treatment for chlamydia. However, because incidence studies have demonstrated that previous chlamydia infection increases one's probability of becoming reinfecting,<sup>46</sup> the CDC does recommend that previously infected individuals be rescreened at 3 months after treatment for chlamydia.<sup>38</sup>

The choice of the several commercially available NAAT assays available is dependent upon preference of the laboratory, as all of these NAATs are mostly comparable in sensitivity and specificity. All NAATs have vastly higher sensitivity compared to older assays, such as enzyme immunoassay direct fluorescent antibody, culture, and point-of-care assays, and have near perfect specificity. NAATs are highly recommended for screening programs because of their higher sensitivity; the older technologies cannot be used for noninvasive specimens, such as urine and vaginal swabs, which are highly desirable for screening programs.

### TRICHOMONAS VAGINALIS

It is estimated that there are 170 million cases for *Trichomonas vaginalis* in the world and approximately 7–8 million new cases occur every year in the United States.<sup>47,48</sup> *Trichomonas* infections have been associated with adverse birth outcomes, low birth weight, premature rupture of membranes and with HIV transmission.<sup>49–52</sup> The identification and treatment of trichomonas during pregnancy can reduce neonatal transmission and may reduce risk of preterm delivery.<sup>53</sup> Trichomoniasis has primarily been screened for at gynecologic visits in the antenatal or family planning setting by visualization of the trichomonads on wet mount microscopy, but this method is relatively insensitive; culture is more sensitive. A relatively new POC test shows promise with better sensitivity than wet preparation and culture.<sup>54</sup>

At present there is no FDA cleared commercial NAAT assay for trichomonas. Several research PCR assays have been reported and appear to perform with sensitivities >90%; greater sensitivity than wet preparation or culture.<sup>54–61</sup> There is one commercially available analyte specific reagent (ASR) (GenProbe) that is FDA cleared for purchase of reagents, but not in a “kit” format.<sup>61</sup> Clinical trials for FDA clearance of this NAAT assays are underway.

Sensitivity and specificity of wet-preparation microscopy for TV are estimated to be between 50–60% and >90%, respectively, whereas sensitivity and specificity of PCR for TV have been shown to be both >90%, respectively.<sup>58,59,62</sup> A study of multiple etiologies of cervicitis in STD clinics, using both a TMA-based research NAAT<sup>61</sup> and another research PCR-based NAAT<sup>57</sup> for trichomonas, demonstrated an overall prevalence of 15.3% for TV compared with 11.9% using wet-preparation microscopy.<sup>63</sup> Because of the lower sensitivity of the wet-preparation method for diagnosis of TV, a significant percentage of infections may be routinely missed, which allows for sexual transmission to partners, as well as discomfort and possible harmful sequelae in untreated women. In a large study of over 3000 women

attending two STD clinics, Kaydos et al. found a prevalence of 17% using PCR against a reference standard of wet-preparation microscopy and culture.<sup>59</sup> The increased sensitivity of NAAT assays in women above traditional methods of diagnosis such as wet preparation are evidence for more future use of NAAT assays for the diagnosis of trichomonas.

### SYPHILIS (*TREPONEMA PALLIDUM*)

Syphilis screening is important to prevent long term sequelae in infected persons, to prevent transmission to partners, and to prevent congenital infections.<sup>64</sup> Screening is inexpensive and should be performed in all at risk populations. Ideally, it should be performed in the first and third trimester in pregnancy.<sup>38</sup> Syphilis screening is part of routine antenatal care in many countries. Syphilis infection during pregnancy can result in vertical transmission to the fetus (transplacental or intrapartum), with 70–100% transmission rates for primary/secondary syphilis and 40% for early latent syphilis.<sup>65</sup> Congenital syphilis can result in fetal wastage (spontaneous abortion, stillbirth), and birth defects ranging from low birth weight to multi-organ system involvement, such as hepatosplenomegaly and glomerulonephritis, as well as growth abnormalities.<sup>65</sup>

Screening for syphilis in the absence of clinical manifestations is an important part of detection, cure, and prevention of vertical transmission. Variability in clinical presentation of syphilis makes clinical diagnosis unreliable.<sup>64</sup> Thus screening must be performed in the absence of symptoms. The classic painless ulcerated lesion has a diagnostic sensitivity of only 31% and specificity of 98%. Induration is reported to be the single most specific sign, occurring in 47–92% of infected persons. Painless regional lymphadenopathy may occur in up to 80% of patients. There are no clinical manifestations associated with early latent, late latent, or syphilis of unknown duration.

Screening by VDRL or rapid plasma reagin (RPR) has a sensitivity of 80% in primary syphilis, 100% in secondary syphilis; in latency the cardiolipin antibody falls and levels are expected to subside after treatment.<sup>64</sup> After treatment for primary or early secondary syphilis, anticardiolipin antibody levels generally fall to nonreactive over 1–2 years.<sup>64</sup> Treatment of latent or late syphilis is usually followed by persistence of a positive RPR.

The VDRL and RPR tests also have variably compromised specificity, leading to biological false positives. Ideally, individuals with positive RPR or VDRL should have subsequent FTA (fluorescent treponemal antibody absorption test), MHA-TP (Microhemagglutination *T. pallidum*), TPHA (*T. pallidum* hemagglutination assay), or TP-PA (*T. pallidum* particle agglutination assay) testing to confirm the diagnosis of syphilis. High-volume clinical laboratories have begun using automated treponemal tests, such as automated enzyme immunoassays (EIAs) or immunochemiluminescence tests, and have reversed the testing sequence: first screening with a treponemal test and then retesting reactive results with a nontreponemal test. This approach has introduced complexities in test interpretation that did not

exist with the traditional sequence. Patients that are reactive to the treponemal test but nonreactive to the nontreponemal test are a source of confusion as to interpretation.<sup>66</sup> When results are reactive to the treponemal test but nonreactive to the RPR test, persons with a history of previous treatment will require no further management. For persons without a history of treatment, a second, different treponemal test should be performed. If the second treponemal test is nonreactive, the clinician may decide that no further evaluation or treatment is indicated, or may choose to perform a third treponemal test to help resolve the discrepancy.<sup>66</sup>

The CDC, United States, recommends that all pregnant women be screened for syphilis at their first antenatal visit, and in settings where antenatal care utilization may not be regular, women may be screened and treated based on reactive RPR-card test.<sup>38</sup> Additionally, it is recommended that high-risk women be screened again during their third trimester and again at delivery.<sup>67</sup>

## GENITAL ULCERS

Nonvesicular genital ulcers can be caused by syphilis, chancroid, lymphogranuloma venereum, donovanosis, or atypical genital herpes. Due to the lack of adequate diagnostic assays, screening for chancroid, and donovanosis is not usually undertaken in asymptomatic persons. Chlamydia NAAT assays can be used for detection of specimens from symptomatic patients with suspected LGV. All commercial NAAT assays will give a positive result for the LGV serovars of *C. trachomatis*. Rapid screening, such as VDRL or RPR, may be performed to screen asymptomatic persons for syphilis. Chancroid may be considered once syphilis has been ruled out by lack of *T. pallidum* visualization on dark field or by negative serology. Chancroid can be confirmed by identification of *Haemophilus ducreyi* by culture.

There is no molecular test commercially available to test ulcer exudates and culture is not routinely available in most settings. As there are no serologic or other screening assays for donovanosis, the diagnosis is made based on clinical presentation, resolution of symptoms with antibiotics, or microscopic examination. Similarly, lymphogranuloma venereum may be presumptively diagnosed based on clinical presentation; however commercial NAAT assays for chlamydia will be positive for swabs of ulcers caused by the chlamydia LGV serovars. Serology, using the complement fixation test, has been used in the past to diagnose LGV infections but this test is not widely available and CDC no longer recommends it be used.

Serological screening for past or present genital HSV (HSV-1 or 2) is feasible with several assays (Focus Technologies, Kalon) being available, as well as several new POC assays which hold promise to move screening outside a clinic setting.<sup>18</sup> While manufacturer's cut-off index values work well for sera from the U.S., these assays suffer from low specificity when testing sera from sub-Saharan Africa and when HIV infected persons are tested; many researchers recommend using higher cut-off index values.<sup>68</sup> Presumptive diagnosis of lesions or ulcers caused by

HSV is often made on the basis of clinical presentation and definitive diagnosis may be made by HSV cell culture. Research PCRs have been published, but not available commercially.<sup>69</sup> Development of POC assays are underway and may be possible in the near future.

## Possible Sites of Opportunistic Screening for STIs

### ANTENATAL AND FAMILY PLANNING CLINICS

Family planning clinics and antenatal clinics are often sites of high prevalences of STIs and these opportunities for screening should not be missed, especially since untreated chlamydial and other cervical infections are associated with adverse pregnancy outcomes (premature rupture of membranes, chorioamnionitis), and neonatal outcomes (conjunctivitis, prematurity, low birth weight).<sup>49,70</sup> Additionally, despite the well-known association of sexually transmitted infections with acute pelvic inflammatory disease and tubal factor infertility, there is a growing literature on the postinfectious tubal infertility, which results from "silent" pelvic inflammatory disease that is unrecognized by the patient and the physician.<sup>71</sup>

### SCREENING TO PREVENT TRANSMISSION: HIGH-RISK POPULATIONS

The WHO urges the assessment of STI prevalence among population subgroups who are likely to have high rates of disease as a result of their risk behavior.<sup>72</sup> WHO recommended that the minimum assessment for STIs among women at high risk of infection should include syphilis, chlamydia, gonorrhea, and genital ulcers by examination. Screening for STIs decreases the efficiency of transmission through cure and duration of infectiousness with earlier detection and cure. Propagation of infection and probability of transmission can be affected by the degree to which an individual interacts with other individuals.<sup>73</sup> One definition of this concept focuses on geographically stable aggregations of people whose sexual activity permits continued transmission; members of core groups might be responsible for a majority of transmissions.<sup>73</sup> Another definition refers to STI core members as a small proportion of people who experience frequent STIs or often transmit infection.

Identification of core groups for targeted STI screening and prevention can maximally reduce potential spread of disease. For example, Over et al. estimated that the cure or prevention of 100 cases of gonorrhea in non core groups will prevent 426 cases of future gonorrhea over the next 10 years. Further, curing or preventing 100 cases of gonorrhea among core transmitters will prevent 4278 cases of gonorrhea over the next 10 years. This study highlights the importance of identifying persons who are at high risk for acquiring and transmitting sexually transmitted infections to achieve the greatest effect in preventing continued transmission.<sup>74</sup> The STI prevalence among male clients of female sex workers in Thailand has been found to be 6% for chlamydia



and 16% for gonorrhea.<sup>75</sup> A study of female sex workers in China found prevalence of 32% for chlamydia, 8% for gonorrhea, 14% for syphilis, and 13% for trichomonas<sup>76</sup>; and among female sex workers in Japan 19% for chlamydia and for 33% gonorrhea.<sup>77</sup> Thus, screening and treating populations with highly prevalent STIs should receive the most attention.

Risk assessment for targeted screening program may be more cost-effective, in addition to identifying large numbers of infected persons. A study was undertaken to compare the performance of the WHO risk assessment approach to population-specific risk factors identified among women attending an antenatal clinic in Mwanza, Tanzania.<sup>78</sup> Similar to the performance of the WHO algorithm to identify women with cervical infection, the risk scores of factors specific to these women had poor sensitivity and positive predictive value for diagnosing cervical chlamydia or gonorrhea infection, though the theoretical cost per true case detected was cheaper.<sup>78</sup> The authors concluded that while it was of primary concern to develop inexpensive diagnostic assays for these infections, risk assessment was feasible and acceptable.

The major limitation of screening recommendations based on demographic and behavioral factors for the identification of STIs is their lack of generalizability. Sensitivity and specificity of risk factor profiles are dependent on population structure, prevalence of infection, and diagnostic laboratory assays being used. Cost-effectiveness depends on the prevalence of infection, the cost of the method(s) used, and the positive predictive value of the screening algorithm. Therefore, specific guidelines may be inappropriate to apply and difficult to compare between different populations; screening recommendations may be most useful when individualized to a particular population.

### ALTERNATIVE SCREENING VENUES OUTSIDE CLINIC

An advantage of using NAAT assays for the detection of chlamydia and gonorrhea is to be able to move outside a health clinic as well as to use the same sample type for the detection of both chlamydia and gonorrhea. While many outreach screening studies have used NAATs primarily for chlamydia testing, being able to additionally screen for gonorrhea has distinct advantages, especially in populations and regions which have demonstrated high prevalences for gonorrhea in the past.<sup>79,80</sup> These alternative sites for screening programs have included schools, prisons, military personnel, health vans, shopping malls, household surveys, street outreach sites, and teen centers.<sup>81–91</sup> One population study surveyed inner city adults 18–35 years of age in their homes and demonstrated a prevalence of 3.0% for chlamydia, 5.3% for gonorrhea, and an overall weighted prevalence estimate of 7.9% for either infection, the majority of which (94.7%) were asymptomatic.<sup>92</sup> Such studies give public health officials the ability to direct future control efforts towards populations where high prevalences of disease exist in asymptomatic and untreated persons not ordinarily seeking healthcare.

Hospital emergency departments have been the site for screening programs in young adults presenting for reasons

other than reproductive healthcare and have demonstrated high prevalences using urine screening.<sup>79–81</sup> Expanding to wide spread screening programs of sexually active individuals using NAAT assays are supported by recommendations of public health officials.<sup>37</sup> Finally, the effectiveness of expanded screening programs in being able to reduce chlamydia prevalence has been shown in areas where the screening programs have been in existence for an extended time.<sup>82</sup>

### Screening to Prevent Cancer: Human Papillomavirus and Cervical Cancer

It is estimated that nearly 100% of cervical cancers are associated with human papillomavirus (HPV).<sup>83</sup> No significant variation in HPV positivity occurs among countries but rates of cervical cancer vary widely.<sup>83</sup> Longitudinal data from developed countries show decrease in cervical cancer incidence and mortality subsequent to the implementation of program for screening and treatment. However, findings from cervical cancer screening program in developing countries acknowledge the economic and infrastructure barriers to regular and opportunistic cervical cancer screening in these developing countries. HPV testing has augmented the PAP smear screening program in the United States recently. However, in developing countries this option is not feasible. Presently, visual inspection-based approach is recommended as the immediate option in resource limited countries. This recommendation is supported by a recent cost-effectiveness analysis comparing visual inspection methods to colposcopy and HPV testing in low-resource settings.<sup>84</sup> Screening every 1–5 years, as in developed countries, is not a practical recommendation in the developing country settings, and it is recommended to screen women aged 35–50 years at least once before providing repeated screening. A mathematical modeling study comparing cervical cancer screening strategies in resource poor settings supports this recommendation.<sup>85</sup> Compared to more frequent screening strategies, screening women aged 30–59 years once in their lifetime could decrease cervical cancer incidence up to 30%, having the greatest effect per resource utilization.<sup>85</sup>

### Future Directions of Screening: Opportunistic Screening

Early detection and prevention of STIs are cost-effective public health measures. Nevertheless, implementation of screening program throughout the healthcare system and outside is difficult. Major barriers include low priority for STIs, inadequate public health surveillance measures, and inadequate resources. Other barriers include societal sensitivities about sexuality, the traditionally curative rather than preventive focus of healthcare, and healthcare inefficiencies that hinder these programs.

Until recently, available STI screening tests have had poor sensitivity and specificity, or have been too difficult to implement on a wide scale. The development of noninvasive, highly sensitive and specific diagnostic techniques has made identification and

**Table 109.1:** Tests for Screening of Sexually Transmitted Infections

Patient	Method	Tests	Sample type
Women	Microscopy	Gram stain for cervicitis and gonorrhea Gram stain for bacterial vaginosis Wet preparation for trichomonas Cytology (PAP)	Endocervix Vagina
	Culture	Gonorrhea Chlamydia Trichomonas	Urethra, endocervix, rectum, pharynx
	Antigen detection or NAAT	Test for chlamydia or gonorrhea	Urethra, first catch urine, endocervix, vaginal swabs
	Serology	Syphilis, HIV, hepatitis B, hepatitis C	Vein Finger stick (Dried blood spots) Oral fluid (HIV)
Heterosexual men	Microscopy	Gram staining (gonorrhea)	Urethra
	Culture	Gonorrhea Chlamydia Trichomonas	Urethra, pharynx
	Antigen detection or NAAT	Gonorrhea Chlamydia	First catch urine Urethra
	Serology	Syphilis, HIV, Hepatitis B, Hepatitis C	Vein Finger stick (Dried blood spots) Oral fluid (HIV)
Men who have sex with men (MSM)	Microscopy	Gram staining (gonorrhea)	Urethra
	Culture	Gonorrhea Chlamydia	Urethra, pharynx
		Gonorrhea, Chlamydia	Rectum
	Antigen detection or NAAT	Gonorrhea Chlamydia	First catch urine, urethra
	Serology	Syphilis, HIV, Hepatitis B, Hepatitis C	Vein Finger stick (Dried blood spots) Oral fluid (HIV)

NAAT: Nucleic Acid Amplification Tests

[Source: www.aidsctc.org]

treatment of gonorrhea and chlamydia feasible on a population basis.<sup>16,35</sup> NAATs can be used to screen urine for chlamydia and gonorrhea (Table 109.1) with sensitivity of 93–98% and specificity greater than 99%, with a high positive predictive value, even in low prevalence populations. These easily administered tests can be used to screen high-risk populations that are otherwise difficult to assess. Admittedly, the high cost of NAATs technology may be prohibitive, and the source of payment remains an issue.

The advent of these noninvasive screening assays may allow for STI screening in nontraditional venues and among expanded populations. For example, in the United States, school-based screening among adolescents,<sup>46,86</sup> and screening of incoming military recruits have demonstrated significant prevalence of undetected gonorrhea and chlamydia infections.<sup>87,88</sup> Screening among persons entering into detention facilities<sup>89</sup> and routine sex worker examinations may detect a significant number of infections. In addition to expanding access to broader populations, urine-based diagnostic assays may overcome barriers to seeking healthcare for genitourinary symptoms, especially among women<sup>90,91</sup>

## Conclusions

Screening for STIs among asymptomatic persons, as well as those with syndromic presentations is essential to prevent the complications of these infections and further transmission. Screening women seeking antenatal and family planning care may maximally reduce reproductive tract and neonatal morbidity for women and their children. Additionally, screening for STIs among high prevalence population subgroups, such as persons who exchange sex for money or drugs, their clients, and persons with multiple sexual partners, can reduce transmission. The greatest barriers to screening remain in accessing populations in a culturally relevant manner. The availability of new noninvasive specimen types and molecular tests will facilitate testing strategies for screening programs.

Performing population and epidemiologic surveys to identify groups of women and men at highest risk of being infected will be useful to target selective screening algorithms for specific populations. Selective screening of persons at highest risk of

being infected will improve the effectiveness of screening. The integration of routine STI screening and treatment, along with comprehensive programs for education, prevention counseling, and partner notification, will be necessary to affect worldwide increasing trends in STI prevalence.

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## Human Papillomavirus Related Genital Neoplasias

### INTRODUCTION

This chapter will largely focus on human papillomavirus (HPV) related genital neoplasias. Human herpes virus 8 (HHV) and associated Kaposi sarcoma is already covered in Chapter 35, while hepatitis B virus (HBV) and associated primary hepatocellular carcinoma is addressed in Chapter 32.

HPV is actually the first pathogen to be recognized as virtually a 100% cause of a specific cancer, that of the cervix. In fact, the story of linking a sexually transmitted agent to cervical cancer started hundreds of years ago, when it was realized that Catholic nuns rarely suffered from this disease.<sup>1,2</sup> Subsequently, around 30 years ago now, and with the tools of molecular biology and sophisticated epidemiological methods, oncogenic genotypes of HPV were proven to be the causative agent of cervical cancer.<sup>3</sup> While there are over 200 genotypes of HPV recognized to date, with well over a hundred already sequenced, around 40 types specifically have tropism for the genital area, with around 12–14 having oncogenic potential.<sup>4</sup> More specifically, it has been shown worldwide, that HPV genotypes 16 and 18 are more virulent, consistently causing around 70% of all cervical cancers,<sup>5–7</sup> and tending to be seen in younger women than with cervical cancers caused by other oncogenic types.

This story is in contrast to many other sexually transmitted infections, where we may know the causative agent, are able to culture the pathogen *in vitro*, have specific antimicrobial agents for treatment, and (apart from HBV, a proportion of cases which are transmitted sexually), despite many attempts, vaccines have not been successfully developed and instituted into public health programs as has occurred for HPV. This is further detailed in Chapter 15.<sup>8</sup> Recognition for the discovery that HPV is the causative agent in virtually all cases of cervix cancer resulted in Professor Harold zur Hausen of Germany being awarded the Nobel Prize for Medicine and Physiology in 2008, bringing the idea that there could be effective vaccines against a cancer into the global public arena worldwide.<sup>9</sup>

### HPV VIROLOGY AND NATURAL INFECTION

The virology, the natural history, and epidemiology of genital HPVs, as well as the clinical manifestations and management are already covered in Chapters 29 and 30, respectively.<sup>10,11</sup> Of note, HPV remains uncultivable by traditional viral culture techniques. Moreover, while genital HPV infection is extremely common, particularly among young, sexually active women, cervical cancer is a relatively rare outcome of HPV infection. Therefore, although the presence of HPV might be a necessary factor, it is not sufficient for carcinogenesis, as only a proportion of women with chronic oncogenic HPV infection will progress over years to develop cervical cancer.

Basically, HPV infects squamous epithelium with expression of various gene products intimately linked to epithelial cell differentiation. HPV infection does not cause a systemic infection; it does not kill the keratinocyte it infects, and it induces no or a poor, slowly developed local inflammatory response. Humoral immunity does not appear to be as important as cell-mediated immunity in clearing HPV infection, but rather is important in protecting an individual from becoming infected. Of note, in natural infection, only around 50% of those becoming HPV DNA positive show a systemic neutralizing antibody response. The remainder of individuals clears infection without developing a measurable antibody response.<sup>12</sup> In addition, of those who become infected with HPV (as detected by HPV DNA), only a small proportion of women will develop a persistent (defined as finding the same genotype on two or more occasions with at least 6 months apart) infection.

Following infection of basal epithelial cells, the viral genome is maintained as a low copy number episome in cells of the basal and parabasal layers and is amplified as the infected cell differentiates and migrates towards the epithelial surface. It is only in the most superficial layers of the epithelium, that late genes encoding for viral capsid proteins (L1 and L2) are expressed and the amplified genomes then packaged into infectious virions, with release at the epithelial surface during cellular desquamation, ready to infect another individual.<sup>13</sup> It is because of this complex interaction of viral maturation with squamous cell differentiation, that HPV



cannot be propagated *in vitro* in cell lines. However, viral nucleic acid can be detected as episomal or integrated genomes by various molecular hybridization assays, as HPV DNA or RNA, and form the basis of detection of HPV infection today. During a productive infection, there is expression of early viral proteins E4, E6, E7 during an infected cell migrating from the basal layer to the epithelial surface, with expression of the major capsid protein L1 following that of E4, and being detectable in poorly differentiated cells at the epithelial surface.<sup>14</sup>

### CELLULAR MANIFESTATION OF HPV INFECTION

Productive HPV infection manifests as low-grade changes cytologically or histologically identified as cervical intraepithelial lesions. If cell mediated immunity fails to induce lesion regression and viral clearance, then persistent infection may result. Really low-grade cervical intraepithelial neoplastic (CIN 1) lesions represent the cytopathic effect of a viral infection and cannot be distinguished accurately from “HPV infection” alone (see Fig. 110.1 for colposcopic findings for HPV infection and in contrast to the normal healthy cervix in Fig. 110.2). It is now realized that it does not necessarily represent a continuum to high-grade disease and cancer, as was once thought. For CIN 1 all early proteins are expressed, the lesions are genetically stable and regression occurs in the majority of cases, with an appropriate host immune response (median duration of CIN 1/LSIL is 6 months).

### ONCOGENICITY

The odds ratios (ORs) for oncogenic HPVs and cancer development are very high, being over 100-fold (281.9 for HPV-16 and 222.5 for HPV-18).<sup>5</sup> This is, in contrast, the elevated OR for cigarette smoking and lung cancer for women which is near 10-fold. Other recognized cofactors that may act in conjunction with oncogenic HPV infection to increase the risk of ICC include cigarette smoking, younger age at first intercourse, high parity, long-term use of oral contraceptive pills, and other sexually transmitted infections (e.g., *Chlamydia trachomatis*, anogenital

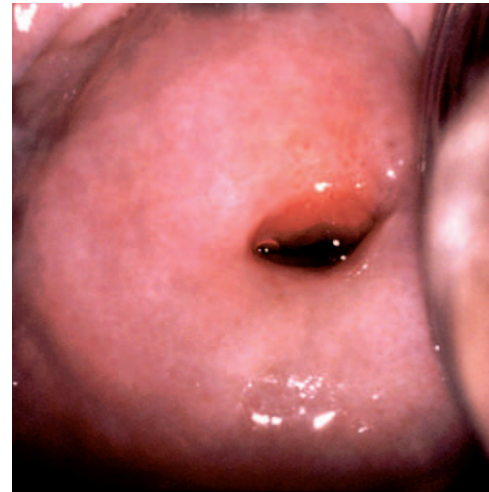


Fig. 110.2: Normal healthy cervix.

herpes simplex).<sup>15–17</sup> However, in general, most of these cofactors had ORs in the order of 2, and could reflect residual confounding due to HPV infection and sexual activity.

With oncogenic HPV infection, there can be progression from productive infection to cellular transformation leading to cervical cancer; then the viral DNA can become integrated into the host cell genome (often with deletions in the E2 and L1 genes), resulting in loss of the ability to produce infectious virions. Not all cancers, however, have integrated virus: some having episomal forms, while others mixed integrated and episomal, while some only episomal. In cancers, the viral gene expression is dysregulated, with constitutive expression of the early oncogenes E6 and E7 essential for progression to, and maintenance of malignancy. Oncogenic genotypes of HPV E6 and E7 oncoproteins specifically bind to important host tumor suppressor factors, P53 and retinoblastoma gene product (Rb), respectively, inactivating their function and resulting in abrogation of control of normal cell growth.

### OUTCOME FOR THOSE WITH PERSISTENT ONCOGENIC HPV INFECTION

In a small proportion of women infection remains persistent, remaining unchanged for years. It is persistent infection with an oncogenic virus which puts a woman at risk from development of high-grade dysplasia. Moreover, it has been shown in separate studies, one in Denmark and one in the USA, that those infected with high risk (HR) HPV (as measured by Hybrid Capture 2 test [HC2]) at baseline with a normal Pap and followed over 10 years, the risk of cytological abnormality of atypical squamous abnormalities or worse at 5 years was almost identical at around 17% and for CIN2+ it was 11%.<sup>18,19</sup> Looking at the 10-year positive predictive value of a single positive HR HPV DNA for cytological prediction of CIN3+ it was around 20%.<sup>18,19</sup> When evaluating outcome for those with 2 HR HPV tests at 5 and 10 years, this risk increased from 8.5% (95% CI, 5.7–11.3) to 20% (95% CI, 14.7–24.9), respectively. Of particular note was the value of a



Fig. 110.1: Colposcopic findings for HPV infection.

concurrent high-risk HPV negative test in cytologically normal women: this carried a high long-term negative predictive value being >99% for CIN2+ and CIN3+, suggesting that the screening interval might be safely increased.<sup>18</sup>

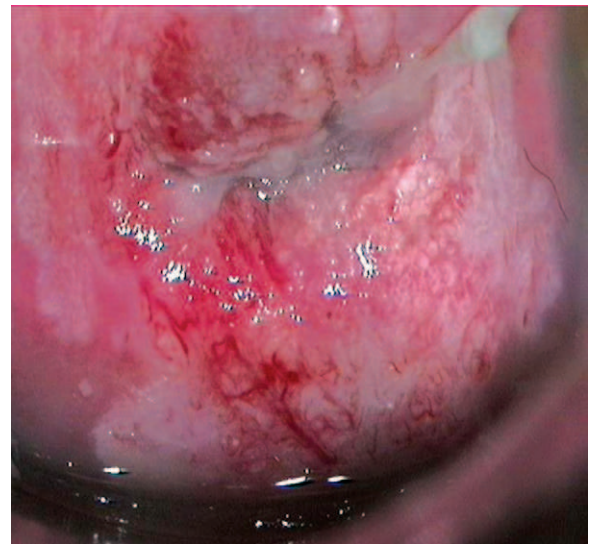
In addition, in looking specifically at an HPV test that distinguishes genotypes, detecting HPV 16 and 18 infections from the other potentially oncogenic types may better identify women at risk for developing CIN 3.<sup>20</sup> In a US study, HPV 16 and the phylogenetically related types HPV 31 and 33, consistently conferred the next greatest risks.<sup>21</sup> Similarly in a Danish study of approximately 11,000 women 20–29 years, with follow-up at ~2 years, and as compared with women who were negative for HPV at enrolment, for those with positive results, there was a significantly increased risk at follow-up of having atypical cells (odds ratio 3.2, 95% confidence interval 1.3–7.9), low-grade lesions (7.5, 4.8–11.7), or high-grade lesions (25.8, 15.3–43.6). Similarly, for those women still positive at the second examination, there was a strongly increased risk of low (34.3, 17.6–67.0) and high-grade lesions (60.7, 25.5–144.0). For high-grade lesions the risk was strongly increased if the same virus type was present at both examinations (813.0, 168.2–3229.2).<sup>22</sup>

### THE TRUE PRECURSOR LESION TO CERVICAL CANCER: CIN 3

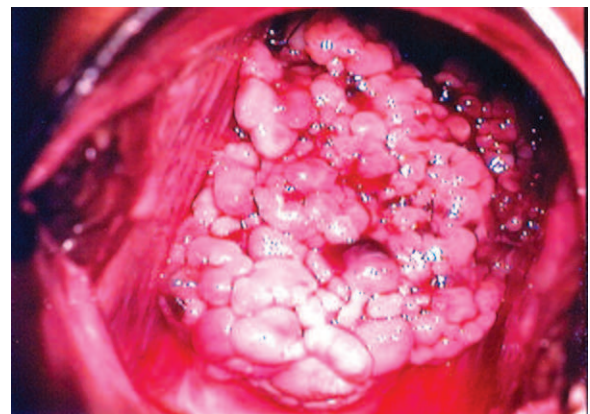
It is now realized that the true precursor lesion to cancer is high-grade cervical intraepithelial neoplastic lesions (CIN 3) with CIN 2 being a mixture of CIN 1 and CIN 3. Hence, it is now accepted that CIN 2 or CIN 3 can occur *de novo*, rather than result as a progression from CIN 1 lesions. The potential differences between CIN 2 and CIN 3 are further exemplified in the trial based quality control assessment of community pathology, biopsy diagnosis, whereby the authors demonstrated detection of CIN 2 generally had poor reproducibility as compared with that of CIN 3.<sup>23</sup> Moreover, although it is realized that persistent infection with oncogenic HPV is a prerequisite the development of CIN 3, not all of these precursor lesions if untreated would become neoplastic. For example, in a retrospective data from women diagnosed with CIN 3 between 1955 and 1976 in New Zealand, and managed only by punch or wedge biopsy, no ablative treatment *per se* the 30-year cumulative incidence of invasive cervical cancer was 31% (95% CI, 23–42).<sup>24</sup> However, it is currently recommended that all high-grade precancerous lesions receive adequate ablative treatment as we do not know which high-grade lesions will regress and which will progress.<sup>24</sup> In general, CIN 3 is asymptomatic, being noted firstly by abnormal cells on a Pap smear, with abnormal features on colposcopy (see Fig. 110.3). Cervical cancer may present with abnormal bleeding, discharge, or complications of advanced disease. Cervical cancer typically arises in the transformation zone. (The findings on colposcopy can be seen in Fig. 110.4 a and b). Although not well understood, the determinants of HPV persistence and progression are likely to be genetic and/or environmental factors.



**Fig. 110.3:** Cervical intraepithelial neoplasia (CIN) 3. Showing areas of aceto-whitening, abnormal vasculature.



\*c+



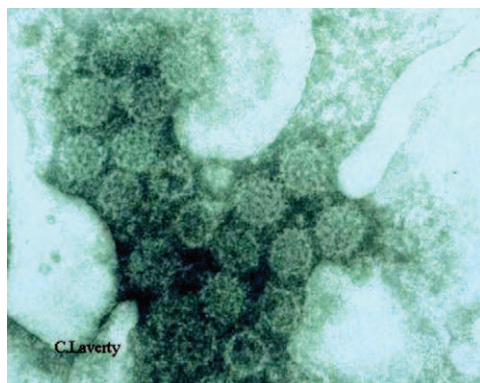
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**Fig. 110.4:** Colposcopy findings of cervical cancer showing abnormal architecture, abnormal vasculature.

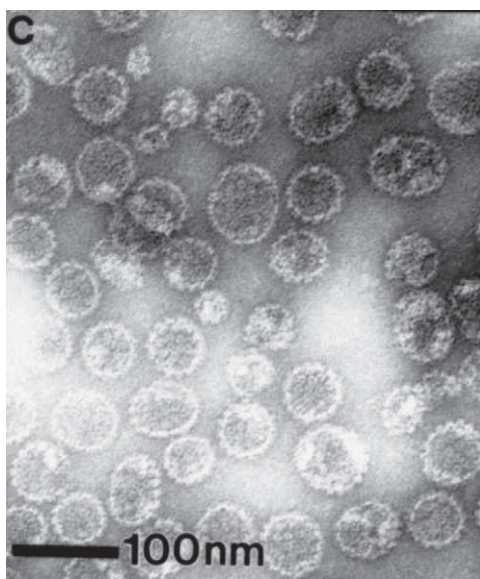


## OPPORTUNITY FOR PREVENTION: PROPHYLACTIC HPV VACCINES

The discovery that the HPV late protein gene (L1 gene) which encodes for the outer viral capsid, when expressed in a vector such as eukaryotic cells (*Saccharomyces cerevisiae* yeast cells or *Spodoptera frugiperda* ovarian cells, the natural host for baculovirus) self assemble and produce empty viral capsids into so-called 'viral-like particles' (VLPs) has underpinned the success of the first generation prophylactic vaccines. Basically VLPs effectively mimic a natural HPV viral infection, but are not infectious, given that they do not contain any DNA and virtually trick the immune system into producing neutralizing antibodies<sup>25–27</sup> (see Fig. 110.5a for electron micrograph of the native HPV virions and Fig. 110.5b for the typical structure of VLPs).



\*c+



\*d+

**Fig. 110.5:** (a) Electron micrograph of the native HPV virions (Printed with permission. Courtesy: Dr. Colin Laverty, Sydney, New South Wales, Australia). (b) Electron micrograph of the typical structure of viral-like particles (Courtesy: Prof. Margaret Stanley, Cambridge, UK).

Currently licensed in more than a hundred countries each, are a bivalent (contains VLPs of 16, 18) vaccine as well as a quadrivalent (contains VLPs of 6, 11, 16, 18), both of which have been shown to be efficacious against precancerous lesions (as surrogates to cancer), as well as against persistent infection of the vaccine related types in those previously naive to these genotypes.<sup>28–30</sup>

Moreover, these vaccines are being implemented as public health tools. Where there has been comprehensive and high coverage of the quadrivalent vaccine, with catch-up programs to 26 years, already significant reductions are reported for genital warts in women younger than 27 years, as well as herd immunity being seen in young unvaccinated heterosexual males.<sup>31</sup> In addition, recently reported from a review of Pap abnormalities in Victoria, Australia, a modest but significant decrease in high-grade abnormalities was demonstrated in those women aged <18 years between 2007 and 2009 when the HPV vaccination program was delivered, and compared to the pre-vaccination period.<sup>32</sup>

## Vulvar and Vaginal Cancers

Vulvar cancer is a less common disease, with global incidence rates ranging from 0.1 to 3.5 per 100,000 women for the years 1998–2002.<sup>33</sup> Nonetheless, vulvar and vaginal cancer collectively account for approximately 6% of all gynecological cancers. In contrast to secondary cancer prevention programs for breast and cervical cancers, no screening programs exist for vaginal and vulvar malignancies. The annual progression rate of untreated VIN3 to invasive cancer is at least 10%, whereas for CIN 3 to cancer is approximately 2%.<sup>34</sup> Patients with VAIN have a 2% risk of developing invasive cancer.<sup>35</sup> Diagnosis of vulvar intraepithelial neoplasia (VIN) (see Fig. 110.6a and 110.6b showing the multi-focal nature of disease with areas of hyper- and hypopigmentation) and VAIN is difficult as is their treatment which can be disfiguring, and requires very long term follow-up, as disease recurrence is common.<sup>36</sup>

Vulvar cancer is largely delineated into two distinct clinicopathologic groups based on histology and age of presentation. In older women, the histological type is keratinizing squamous cell carcinoma, which may develop in areas of preceding squamous cell hyperplasia or associated with vulvar dermatoses, particularly lichen sclerosis (see Fig. 110.7). These are not related to HPV infection. In contrast in younger women, the histology is warty, basaloid squamous cell carcinoma, associated with prolonged infection with HPV, particularly type 16<sup>37,38</sup> (see Fig. 110.8). Of particular concern is the changing epidemiology, with increasing number of cases of VIN and vulvar cancer being reported in younger women worldwide.<sup>37,39</sup> Just as cervical cancer, premalignant cellular changes can be found in the vulvar epithelium; these are called VIN. VIN was once graded in three categories from lesser to more severe neoplastic changes (VIN 1, 2 or 3). As low-grade cervical changes, low-grade VIN is really the cytopathic effect of HPV infection and usually resolves spontaneously over time. A small proportion of cases of high-





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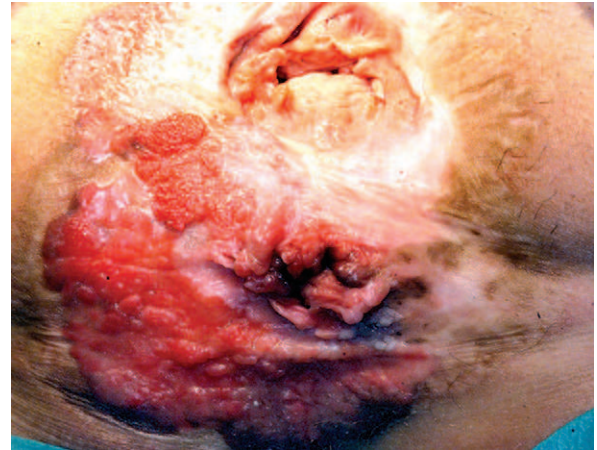


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**Fig. 110.6a,b:** Multi-focal vulval intraepithelial neoplasia (VIN3) with areas of hyper- and hypopigmentation, including involvement of the perianal area in (a) (Printed with permission. Courtesy: Dr. Alice Rumbold, Adelaide, Australia).



**Fig. 110.7:** Large cancerous tumor: rolled edge, friable, bloody, and necrotic with underlying lichen sclerosis (Printed with permission. Courtesy: Dr. Alice Rumbold, Adelaide, Australia).



**Fig. 110.8:** Vulvar cancer in younger woman.

grade VIN (VIN 2 and VIN 3) will progress to invasive vulvar cancer if left untreated. Thus, just as in the cervix, the histological rating system of VIN 1-3 does not necessarily infer a biological continuum. New terminology proposed by the International Society for the Study of Vulvovaginal Disease<sup>40</sup> recommended that the term VIN 1 be dropped, as it does not represent a cancer precursor. In contrast VIN 2 and 3 are considered the preneoplastic lesion of vulvar squamous cell cancer; both lesions express p16(INK4a), a protein product of tumor suppressor gene p16, the aberrant expression of which correlates with the underlying genetic mutations and consequently potential for malignancy. The VIN 2/3 lesions seen in older women (55–85 years of age) are largely differentiated (simple) seen in association with lichen sclerosis and squamous hyperplasia. The undifferentiated VIN associated with persistent high-risk HPV infections, seen in younger women (commonly between the ages of 30 and 40 years), is often multifocal, with a highly variable clinical outcome (see Fig. 110.6). Of note is the strong association with smoking and immunosuppression.<sup>41–43</sup> A proportion of the vaginal cancers are also HPV related (Fig. 110.9).



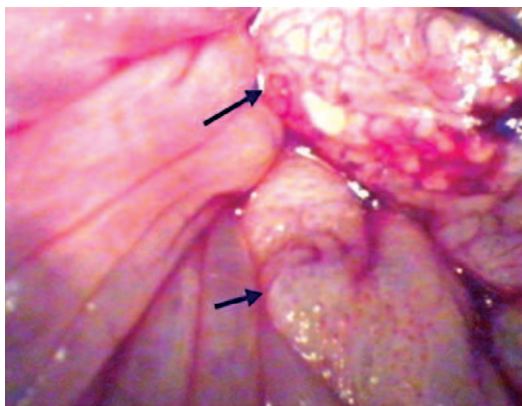
**Fig. 110.9:** Vaginal cancer.

In clinical trials the prophylactic administration of quadrivalent HPV vaccine was highly effective in preventing HPV-16 or HPV-18-related VIN 2/3 or VAIN 2/3 in women who were naïve to these types prevaccination, with an efficacy of 100%. In follow-up of the placebo arm of the same trials, incident infection with HPV-16 was the most common (6 per 100 person-years). The mean duration from incident infection to the development of VIN 1-3 was 18.5 months (95% confidence interval 13.4–23.6). HPV 16 was observed in 64.5% of VIN 2-3 and 6.5% of VIN 1, last HPV 6/11 was observed in 64.5% of VIN 1, 29% of VIN 2-3.<sup>44</sup> Hence in the long term such vaccines should result in reduced rates of HPV-related vulval and vaginal cancers.<sup>45,46</sup>

## Anal and Penile Cancers

While much is known about oncogenic HPVs being the etiological agents of cervical cancer in women, evidence is gathering to show that oncogenic HPVs, particularly type 16, are strongly associated with some anogenital cancers in men (and women). Specifically, HPV has been linked with 90% of anal cancers, approximately 40% of penile cancers, and around 12% of oropharyngeal cancers.<sup>47</sup> In contrast to cervical cancer, these cancers are less common, with penile cancer being rare and constituting less than 1% of all male cancers, and with an incidence rate recorded in Danish men over a 20-year period in the order of 1 per 100,000.<sup>48</sup> HPV is associated with a proportion of the precancerous high-grade dysplastic lesions of penile and anal intraepithelial neoplasias (PIN and AIN, respectively) (see Fig. 110.10).

Given the greater risk and incidence of anal cancer, and the recognition of progression of high-grade anal intraepithelial neoplasia (AIN 2/3) to anal squamous cell carcinoma in HIV-positive men who have sex with men (MSM),<sup>49,50</sup> some clinicians are recommending screening for AIN in HIV-positive MSM and possibly HIV-positive women (and possibly those with other immunocompromised states such as transplant recipients) using anal cytology, high-resolution anoscopy (HRA), with directed HRA biopsy for definitive diagnosis.<sup>51</sup>



**Fig. 110.10:** Anal intraepithelial neoplasia (AIN) as seen at anoscopy.

However, implementing such screening strategies requires cytologists trained in anal cytology, clinicians trained in HRA, as well as appropriate treatment and follow-up of AIN 2/3. In addition, some ablate AIN 2/3 when it is diagnosed, while others keep it under careful surveillance.<sup>50,52</sup> As there are divergent views with respect to screening for and management of AIN 2/3, appropriate guidelines for care are required.

## VACCINATION IN MEN

There is an established body of data which demonstrates the significant role that male HPV infection contributes to infection and cervical disease in women.<sup>53,54</sup> Hence vaccination of young males with prophylactic HPV vaccination should not only result in prevention of HPV-related disease in men, but also to substantially reduce the disease burden in women.<sup>55</sup>

The quadrivalent vaccine has also demonstrated efficacy against disease in heterosexual males and MSM aged 16–26 years.<sup>56,57</sup> In a randomized, placebo-controlled study ( $n = 4065$ ), vaccine efficacy against any HPV 6, 11, 16, or 18-related external genital lesion was 90.4%, and against genital warts and PIN, it was 89.4% and 100%, respectively. In these young males, vaccination was also effective against persistent infection (85.6%).<sup>57</sup> Further analysis of vaccine efficacy in MSM ( $n = 602$ ; aged 16–26 years) confirms the benefits of HPV vaccination in reducing the burden of anogenital HPV infection and the incidence of HPV-related external anogenital warts (79.0%).<sup>56</sup> After 7 months, seroconversion rates for HPV 6, 11, 16, and 18 were  $\geq 89.5\%$ . Data have also recently been reported at the International Papillomavirus Conference in Montréal, 2010 showing efficacy against 16/18 related AIN.

Hepatitis B virus and hepatocellular carcinoma as well as HHV 8 and Kaposi sarcoma are already covered in Chapters 32 and 35.

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# HIV, Sexually Transmitted Infections, and Human Rights

Chris Beyrer • Stefan D. Baral

## Introduction

There is no more private and profoundly personal domain of human activity than sexual life. Violations of sexual rights are among the most egregious of abuses precisely because they affect this most personal realm of life. And because sexual life includes reproduction and the special challenges faced by women in reproduction and in reproductive health; sexual rights are inextricably tied to reproductive rights and to all the contention which have surrounded reproductive issues such as choice, women's autonomy, women's agency in sexual decision making, and individual privacy. It is generally recognized that the universal rights shared by all of humanity have their basis in the essential dignity of our status as human beings.<sup>1</sup> Sexual rights violations then are special threats to human dignity—and they have been misused as such by violators—to degrade, to dehumanize, to strip of dignity. In some conflict settings, sexual violence has been used to terrorize populations through the use of rape as a tool of war, as has been documented in the Former Yugoslavia, in Rwanda, Burma, and, most recently, in DR Congo.<sup>2–5</sup> It is because of the grave nature of these violations that international human rights conventions and laws often provide special protection for sexual rights, reproductive rights, and the sexual health and well-being of women and girls, the most frequent, though certainly not exclusive, victims of sexual rights violations.

The interactions of sexual life, health, and human rights are many and varied, though they have been little studied by the medical professionals. We will explore four contexts in which HIV/AIDS and other sexually transmitted infections (STIs) have been shown to have important associations with human rights contexts, and where examples of population-level interactions appear to be of both public health and human rights significance.<sup>6</sup> These areas are HIV, STIs, and the rights of migrant populations; HIV and STIs in conflict settings; trafficking and coerced sex work; and the special vulnerabilities of sexual minority populations, including men who have sex with men in settings of homophobia and discrimination. To explore these domains the basic components of the human rights framework is essential.

There are several underlying assumptions to the use of the human rights framework. First, it is arguable that human rights abrogation or protection can have profound impacts on the health of individuals, communities, and populations. The evidence base for these interactions is increasingly emerging, but it must be said that human rights have been little studied as health determinants in the STI area, whereas there are more studies, and more interest generally, in the HIV/AIDS literature.<sup>7,8</sup> This is due to both more scholarly interest, the foundation of which has been significantly attributed to the late Jonathan Mann, and to the earlier and intense interest in civil and health rights, and in human dignity more broadly, among affected populations, including gay men in the developed world, and people living with HIV/AIDS more globally.<sup>9</sup>

Second, sexual rights violations are a subset of threats to human dignity—forced, coerced, and related higher risk sexual exposures are correlated with adverse sexual and reproductive health outcomes—including STIs. There are the mechanisms at play in these interactions which need further study, but which nevertheless are clear enough to merit interventions.<sup>10</sup> And finally, responses which include human rights understandings and which seek to improve the rights contexts for people at risk may improve HIV/STI prevention, treatment and control, and provide measurable benefit in human rights contexts for those at dual risk. The challenges of developing and evaluating rights-based interventions and programs for HIV and STI are substantial, but the benefits to individuals, their partners and families, and to communities may be considerable.

## Relevant Human Rights Conventions for Sexual Rights, HIV, and STI

The modern human rights movement had its origins in the same atrocities as did modern medical ethics: the crimes against humanity perpetrated by the national socialists in Germany and their allies during World War II. In response to the Holocaust and the crimes of Nazi doctors, the United Nations General Assembly adopted a visionary set of principles articulating those

fundamental rights of human beings which no state could take away. These were articulated in the 1948 Universal Declaration of Human Rights (UDHR).<sup>1</sup> Delegates representing the United States to the UDHR drafting committee included first lady Eleanor Roosevelt and the great African American scholar W.E.B. Du Bois. Each succeeded in achieving inclusion in the UDHR, respectively, of full and equal rights for women, and full and equal rights for all racial and ethnic minorities. That the United States would endorse the latter principle during the 1940s, when much of the country remained under Jim Crow segregation statutes, illustrates how painfully far so many countries had to go in realizing these universal rights at the time of the Declaration. Nevertheless, the UDHR remains an essential founding document of human rights law and policy. It was an aspirational document, however, not an enforceable treaty. It has no monitoring mechanism and no way to hold violators accountable for rights abrogation.

The UDHR says little specifically in regard to health, but does articulate in Article 25 that all persons have a right to a minimum standard of living, which includes access to healthcare:

“... Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care and necessary social services, and the right to security in the event of unemployment, sickness, widowhood, old age or other lack of livelihood in circumstances beyond his control...”

The human rights document which does speak most specifically to the right to health is the 1976 International Covenant on Economic, Social and Cultural Rights (ICESCR), again of the United Nations.<sup>11</sup> Article 12 of the ICESCR refines the right to health with new precision:

Article 12:

1. The states parties to the present Covenant recognize the right of everyone to the enjoyment of the *highest attainable standard* of physical and mental health.

The steps to be taken to achieve the full realization of this right shall include:

- (a) The provision for the reduction of the still-birth rate and of infant mortality and for the healthy development of the child.
- (b) The improvement of all aspects of environmental and industrial hygiene.
- (c) The prevention, treatment, and control of epidemic, occupational and other diseases.
- (d) The creation of conditions which would assure to all medical service and medical attention in the event of sickness.

An amendment to this convention, General Comment 14, was made in 2000, in part to address the special issues raised by the AIDS pandemic.<sup>12</sup> Article 8 of the general comment speaks both

to a more precise explanation of the right to health, and of the right to sexual and reproductive freedom:

The right to health is not to be understood as a right to be *healthy*. The right to health contains both freedoms and entitlements. The freedoms include the right to control one's health and body, *including sexual and reproductive freedom*, and the right to be free from interference, such as the right to be free from torture, non-consensual medical treatment and experimentation.

Two other conventions deserve special mention in regard to sexual rights. The international convention on civil and political rights (ICCPR) of 1976 and the convention on the eradication of all forms of discrimination against women (CEDAW) of 1981.<sup>13,14</sup> The ICCPR generally deals with political rights, including such basic rights as freedom from slavery, torture, persecution, and discrimination. It includes non-discrimination on the basis of sex as a basic right, but did not directly address sexual orientation. In 1994, the UN Human Rights Committee decided *Toonen vs. Australia*, a case in which the Australian State of Tasmania, which had legislation which allowed discrimination against gay and lesbian citizens, was overturned (UNHRC). The UN ruling was that discrimination based on sex, included sexual orientation, and so was in violation of the Convention. This has expanded the right to freedom from discrimination to sexual minority populations within international human rights law.

CEDAW, the 1981 Convention aimed at gender discrimination articulated a set of principles for women and girls in health services.<sup>14</sup> CEDAW states that health services must be consistent with the human rights of women, and that these rights include: autonomy, privacy, confidentiality, informed consent, and choice. These principles are readily seen as in accord with most ethical standards in developed countries. But limits on women's autonomy and privacy, as examples, are markedly common in many settings, where women may have little say in reproductive choice, and even seeking medical care may require male partner or consent of other family members.

## Human Rights and Vulnerability to HIV and STI

How do violations of the rights described actually impact real human beings? How do human rights violations increase vulnerability to STIs or to HIV? We suggest at least three mechanisms by which these interactions may occur.

- (a) *Increased exposure*: Sexual coercion, sexual violence, the use of rape as a tool of war and the kinds of population mixing seen in some conflicts may all increase the likelihood of those suffering rights violations to experience increased exposure risks for HIV and STI.
- (b) *Increased acquisition and transmission*: Treatment delays or gaps, barriers to access to sexual and reproductive health services, and lack of condoms and contraceptive choice may all lead to increased acquisition and transmission risks for STIs.



- (c) *Increased morbidity and mortality*: Barriers to access and to information may increase the disease severity and long-term sequelae of infections once they occur.

## Mapping Domains

Understanding how human rights abuses or protections impact HIV and other STIs is complex. This is an emerging area of investigation, and requires both research and program efforts to further explore. We have identified several domains where these interactions can be explored, but there are doubtless many others ranging from the risks associated with incarceration to the increased vulnerabilities to infection associated with domestic violence that also require research and programmatic responses. Domains where evidence of rights and HIV/STIs will be explored include migration, conflict, sex trafficking, and the vulnerabilities of sexual minority populations.

## MIGRATION

Throughout recorded history, populations have migrated because of economic changes, social change, war, and travel.<sup>15</sup> Though migrants tend to be healthier than the general population because of the “healthy traveler effect”; where measured, migrants generally carry a disproportionate burden of infectious disease including genital herpes, chancroid, lymphogranuloma venereum, donovanosis, and HIV.<sup>16–25</sup> Given that there are currently between 175 and 200 million people documented as living or working outside of their countries of birth, representing approximately 3% of the world’s population, this is a population requiring attention.<sup>26</sup> This number includes approximately 120 million voluntary migrants, people who have chosen to leave their country of origin, and the other 55–80 million are forced migrants, including refugees, trafficked people, and internally displaced people.<sup>15,27</sup> Moreover, there are multiple modes of migration, including permanent migration, temporary migration such as “oscillating” migrants who travel for work and return home periodically, if circumstances allow, and seasonal migration, generally for work in agricultural sectors.<sup>28</sup> Many countries encourage legal, and do little to combat illegal, immigration of a workforce willing to do the type of jobs that their own populace will not, or at a salary level below the living wage.<sup>29</sup> However, in return the receiving country should be compelled to offer and develop socioculturally appropriate HIV/STI prevention strategies, or at least translate existing education programs to the local languages of the migrants.<sup>27</sup> Recognizing the health needs of migrants, the UN General Assembly adopted the “International Convention on the Protection of the Rights of all Migrant Workers and Members of their Families” in December of 1990.<sup>30</sup>

Article 43 states:

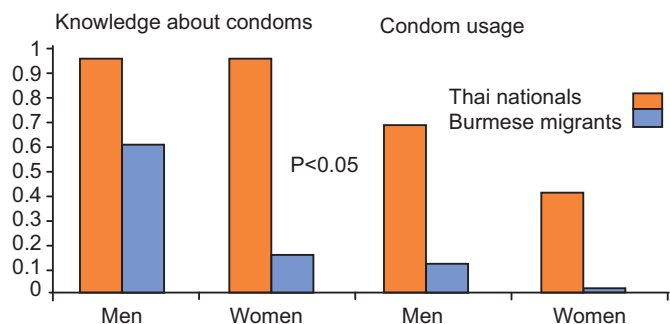
Migrant workers shall enjoy equality of treatment with nationals of the state of employment in relation to:

- (a) Access to educational institutions and services subject to the admission requirements and other regulations of the institutions and services concerned;

- (b) Access to vocational guidance and placement services;  
(c) Access to vocational training and retraining facilities and institutions;  
(d) Access to housing, including social housing schemes, and protection against exploitation in respect of rents;  
(e) Access to social and health services.

To date only 22 countries have ratified the convention, with an additional 10 having signed it. The countries that have ratified and signed the convention tend to be the source or origin countries for migrants and thus these protections only apply to about 2–3% of the global migrant population.<sup>31</sup> Unfortunately, there are far more published examples of governments ignoring the needs of migrants resulting in heightened STI and HIV risk.

Thailand has been heralded as an early adopter of evidence-based HIV and STIs interventions targeting heterosexual and parenteral transmission. In response to knowledge, attitude, and perception (KAP) surveys in the early 1990’s that demonstrated low levels of understanding regarding HIV and STIs transmission routes and high-risk practices, the Thai government developed and operationalized a comprehensive education and awareness program. In just a few years, repeat KAP surveys characterized the success of this programming with much higher HIV and STI-related knowledge in the general population. However, studies completed around that time and since have shown that these messages were not disseminated to the more than 1 million Burmese migrants in western and northern Thailand living outside of the refugee camps.<sup>32</sup> Specifically, more than 95% of both male and female adult Thai nationals understand the role of condoms in prevention the transmission and acquisition of HIV and other STIs. However, less than 60% of male Burmese migrants and less than 15% of female Burmese migrants can answer these same questions correctly ( $p < 0.05$ ). Moreover, 68% of male and 40% of female Thai nationals reported regular condom usage in comparison to 12% of male Burmese migrants and 1.4% female Burmese migrants ( $p < 0.05$ )<sup>32–35</sup> (Fig. 111.1). Qualitative work identified five barriers to information and healthcare among



Barriers to information, health care: Language, legal, physical, economic and political.

PHR/JHU: Thailand's failure to provide access to services violates Thai law AND undermines national HIV and STD programs

**Fig. 111.1** Burmese migrants and barriers to access in Thailand.<sup>32–34</sup>

Burmese migrants: language, legal, physical, economic, and political.<sup>32</sup> Physicians for human rights (PHR) concluded that Thailand's failure to provide access to reproductive health and preventive services violated Thai law and undermined national HIV and STD programs.<sup>35</sup>

After the collapse of the Soviet Union, there was a sharp increase in population mobility, mixing, and migration, and consequent epidemics of infectious diseases such as syphilis and HIV-1.<sup>36,37</sup> There has been a sharp increase in both internal and external migration of sex workers across the former Soviet Union (FSU) with increasing involvement of organized criminal syndicates.<sup>38</sup> Sex workers are believed to play important roles in the emerging sexual risk component of the FSU epidemics, but the data are sparse and research in this area fraught with logistical and human subjects protection challenges.<sup>38</sup> In 2005, our group studied 483 female sex workers in Moscow and found relatively high prevalence rates of STIs including a syphilis rate of 15.8%; *chlamydia trachomatis*, 18.4%; gonorrhea, 2.9%; and HIV, 3.1%. Overall, 34.6% of women had biological evidence of any STI—and after adjusting for age, sexual practices, and education level, a prominent risk factor was determined to be the limited access to healthcare (aOR: 2.1, 95% CI 1.2, 3.5,  $p < 0.01$ ). Since many of these women migrated to Moscow from other states of the FSU, they were not granted a Moscow residency permit which has increased their risk of contracting STIs.

The lack of access to appropriate or evidence-based care in settings where those services are available to the host population is a common determinant of STI and HIV risk for migrant populations. This risk has been demonstrated for Mexican migrants to the United States, Nepalese migrants to India, rural to urban migrants across China, and beyond.<sup>16,21,25,39,40</sup> To counteract this determinant of HIV and STI risk, the WHO has designed a framework for a public health approach for migrants. The essence of this framework is to uphold article 43 of the International Convention on the Protection of the Rights of all Migrant Workers and Members of their Families; avoid disparities in health status and access to health services between migrants and the host population. Secondly, the destination country should uphold the rights of the migrant by limiting discrimination or stigmatization, and removing impediments to migrants' access to preventive and curative infectious disease interventions.<sup>27</sup> Arguably, these two actions would protect the health of the migrant populations, but also the host population given the overlap of social and sexual networks between these two populations.

## CONFLICT AND STI & HIV VULNERABILITY

More people died in conflict settings during the 20th century than throughout recorded history and the 21st century seems to be outpacing its predecessor.<sup>41</sup> Understanding the relative contribution of sexually transmitted infections to conflict-related morbidity and mortality has proven complex. Rights abuses, including violations of the rules of war and the deliberate targeting of civilian populations have long been a feature of war, and in

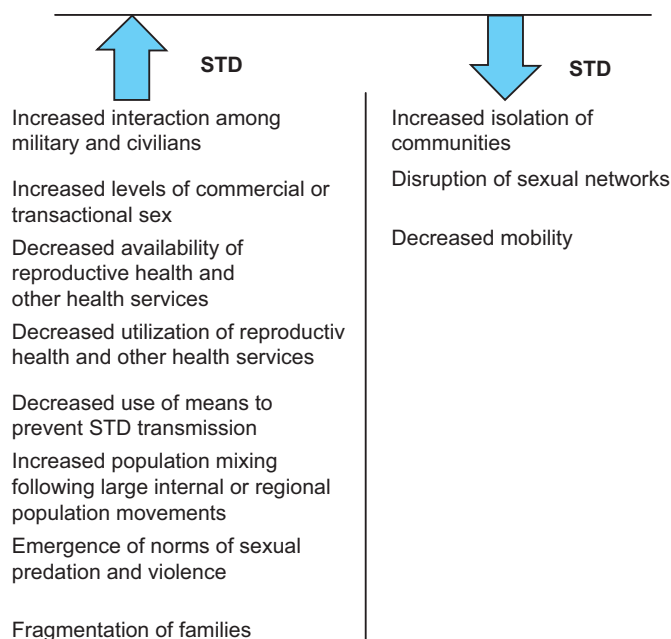


Fig. 111.2 Conflict and STDs.<sup>48</sup>

particular of the kinds of civil conflicts which have generated “complex emergencies,” where humanitarian crises unfold in the context of conflict, exposing civilians to a wide array of abuses. There are a number of structural drivers of sexual and gender-based risks for STI and HIV that may increase transmission risks associated with increased interaction between military and civilians (Fig. 111.2). In the African context, a recent review demonstrated that military personnel tend to have higher HIV prevalence rates than their civilian counterparts.<sup>42</sup> Influx of military personnel has long been associated with increased levels of commercial, transactional, and survival sex.<sup>43</sup> Women and girls are also more likely to engage in survival sex in conflict settings where unemployment is rampant, and most forms of economic productivity interrupted.<sup>44</sup> These types of sex, especially in the context of conflict settings, tend to be associated with lower rates of condom usage than in comparable non-conflict settings.<sup>45</sup>

Conflict can also interrupt health services more broadly, reducing access to care. In the armed conflict of Cote D'Ivoire, between 25% and 55% of the population was displaced depending on region of residence.<sup>46</sup> And in turn over 3 years Cote D'Ivoire experienced a 95% reduction in doctors (234–11); and nearly 80% decrease in allied health professionals (1319–273). Hence, the provision of comprehensive healthcare services in conflict settings is in the very least disrupted, but more commonly is indefinitely suspended.<sup>47</sup> While this tends to include such basic public health interventions as pediatric vaccinations, it also mitigates the availability of reproductive health services to the afflicted population. Condom and lubricant distribution, HIV testing and counselling, and syndromic treatment of STIs are all services affected by conflict.<sup>48</sup> Lastly, antiretroviral management of known HIV-seropositive patients is intermittently disrupted

causing increased morbidity and mortality, with the potential of increased incidence of drug-resistance strains of HIV.<sup>49</sup>

Rape of women and girls has been long a reality of conflict—and in recent conflicts, rape, itself, has been used as a tool of war. Under the convention on the eradication of all forms of discrimination against women (CEDAW) and the convention on the rights of the child, rape is both an egregious human rights abuse, and a violation of the rules of war.<sup>1,14,50,51</sup> In civil wars, such as in the democratic republic of Congo and Darfur, rape has been reported by thousands of women. And these sexual acts have been so violent as to have caused recto-vaginal fistulae in the victims.<sup>52</sup> However, the most extreme example in history is the rape of 250,000 women and girls in just a few months during the Rwandan civil war perpetrated by the Rwandan army and Hutu extremists in 1994. Subsequently, tens of thousands of HIV-positive women reported these rapes as their primary risk factor for HIV acquisition. Though antiretroviral coverage has increased over the last 15 years, the HIV-related morbidity and mortality among these women has been unacceptably high.<sup>53,54</sup>

Recent mathematical models have been developed to characterize the relative contribution of rape during war and found that rape alone is likely not directly responsible for significant increases of HIV/STIs in the general population prevalence. Anema et al. developed models assuming a conflict setting where 15% of women were raped by perpetrators with eight times the prevailing population HIV prevalence and four times the transmission rate per coital act and found only a very modest increase in absolute HIV prevalence of 0.023%.<sup>55</sup> These analyses were informed by whatever raw data were available from conflict settings including Somalia, Sudan, Sierra Leone, among others. The authors conclude that many militias are made up of young men and boys from rural areas, and may not have a high HIV prevalence. However, these models do not take into account secondary effects of rape-mediated HIV transmission including vertical transmission, heterosexual infection of these women's primary male partners, who may have concurrent partnerships, and finally increased susceptibility to HIV acquisition by future partners mediated by genital ulcerative diseases. Whatever the contribution to overall HIV prevalence at population levels, the impact of these crimes against women and girls is profound at the individual, family, and community levels. And such crimes do not need disease associations to be prosecuted. Indeed, part of the case against Charles Taylor, former leader of Liberia, is the use of rape as a tool of terror by forces he supported in the civil conflict in Sierra Leone, and for which is currently standing trial for crimes against humanity by the Special Court for Sierra Leone in The Hague.<sup>56</sup>

Adding to the complexity of assessing the role of conflict in the spread of HIV and STIs is that these contexts can also paradoxically mitigate HIV-related risk. Sexual networks are disrupted, communities are isolated, and mobility limited.<sup>48</sup> These determinants may act to significantly limit HIV spread in the context of generalized epidemics during times of war.<sup>57</sup> But whatever population-level protection from HIV exists during

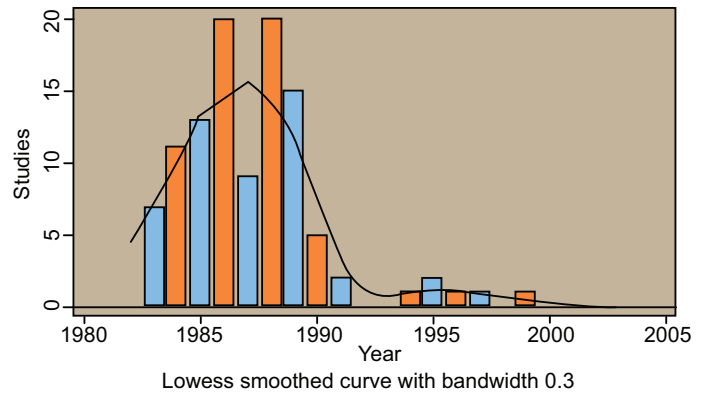


Fig. 111.3 HIV/AIDS studies initiated, DRC, 1982–2004.<sup>59</sup>

wartime, it is arguably outweighed by the immediate increase in population mobility and mixing during the reconstruction phase following the end of conflict.<sup>58</sup>

As described in this section, history is full of examples of the failure of sustained healthcare delivery in conflict zones. A retrospective analysis of HIV/AIDS studies initiated in the Democratic Republic of Congo demonstrated that similar to its neighbors, there was a significant amount of research that took place in the 1980's. However, with the onset of a sustained war in the late 1980's and 1990's, little research has been done there since (Fig. 111.3). And the limited work that has been done has focused on the effects of conflict on HIV/AIDS service delivery.<sup>59</sup> These prolonged conflicts have necessitated the development of practical and evidence-based HIV/AIDS interventions and research strategies for these settings. Mills et al. have shown that it is possible to deliver sustained antiretroviral medications to HIV-infected people in Northern Uganda and achieve compliance rates as in comparable low-income group, but non-conflict, settings.<sup>60</sup> In this study, their group delivered combination antiretroviral medications to 1625 people, 14 years and older, with 92.2% (1403/1521) of patients with adherence data having more than 95% adherence. Another example of service delivery in conflict zones are the mobile obstetric medics (MOM), which provide antenatal care, family planning, syphilis screening, among other health services in Eastern Burma.<sup>61</sup> These examples highlight both the possibility and necessity of the continued provision of comprehensive and sustained health and preventive services during wartime and in conflict zones, above and beyond emergent care.

## TRAFFICKING AND COERCED SEX WORK

Trafficking in persons violates universal human rights to life, liberty, and freedom.<sup>62</sup> It has been defined as a “modern form of slavery,” by Human Rights Watch (HRW, 1996). The subset of trafficking which includes trafficking for work in commercial sex is a particularly heinous form of slavery and one with potential grave, if difficult to study, health implications. The United Nations Palermo Protocol of 2000, “Protocol to Prevent, Suppress and Punish Trafficking in Persons, Especially Women



and Children, Supplementing the United Nations Convention Against Transnational Organized Crime,” addresses trafficking, including sex trafficking and related forms of sexual exploitation, and is now widely used in the field.<sup>63</sup>

Palermo defines trafficking in persons as:

The recruitment, transportation, transfer, harboring or receipt of persons, by means of the threat or use of force or other forms of coercion, of abduction, of fraud, of deception, of the abuse of power or of a position of vulnerability or of the giving or receiving of payments or benefits to achieve the consent of a person having control over another person, for purpose of exploitation.

Exploitation shall include, at a minimum, the exploitation of the prostitution of others or other forms of sexual exploitation, forced labor or services, slavery or practices similar to slavery, servitude or the removal of organs.

The evidence base for the health effects, including impacts on HIV and STI, for sex trafficking is modest but growing.<sup>64–67</sup> In a series of important papers among women and girls trafficked between Nepal and India, Gupta et al. and Silverman et al., have studied the HIV and STIs associations with trafficking in this extensive prostitution context. In a 2007 *JAMA* paper, they reported that girls trafficked into sex work prior to age 15 years were at markedly higher risk for HIV infection than those trafficked at 18 years or older, with an adjusted odds ratio (aOR) of 3.7 (95% CI = 1.32–10.34).<sup>68,71</sup> These younger trafficking victims, albeit a small sample ( $n = 33$ ) had over a 60% prevalence of HIV infection. Having been trafficked to Mumbai, as opposed to other destinations in India, was associated with a markedly higher aOR for HIV infection, as was longer duration of forced prostitution, suggesting structural factors like play key roles in the risks for HIV among these girls and women.

Zimmerman and Watts have done considerable work on sex trafficking into Europe.<sup>70</sup> They recently reported on a series of 192 women in post-trafficking services and found very high levels (greater than 95% of all women interviewed) of reporting of violence and coercion while in trafficked circumstances, and high levels of post-traumatic stress disorder (PTSD) among survivors—suggesting that HIV and STI are part of a larger continuum of health threats for these women and girls.<sup>71</sup>

There is no debate that sex trafficking is a grave threat to the health and well-being of its victims. But there is considerable debate about the scale and scope of this health threat, and about the relationship of sex trafficking to sex work more broadly.

In an investigation conducted by our group in collaboration with Physicians for Human Rights on trafficking among Burmese and Ethnic Minority women and girls in Thailand, we found that trafficking was much less common than had been reported in the lay media, and that sex trafficking was a relatively small component of trafficking from Burma, involving some few hundred cases per

year, while labor migration involved hundreds of thousands of Burmese over the same time period.<sup>34</sup>

The relationship of sex trafficking to sex work, more broadly, has been an intensely contested area for the public health community.<sup>72,73</sup> The issue emerged in the U.S. political sphere with the inclusion of a controversial “Prostitution Pledge” in the initial legislation creating both the President’s Emergency Plan for AIDS Relief (PEPFAR) program and the Office of the Global AIDS Coordinator (OGAC). The language deliberately merged sex trafficking with prostitution writ large, and required all PEPFAR grant recipients to adopt a policy of opposing sex trafficking and prostitution in order to qualify for US federal AIDS funding. There was no debate around opposing sex trafficking, clearly seen as both a crime and severe human rights violation by all relevant parties. The controversial issue was the conflation of all sex work with sex trafficking. In a widely publicized refusal to comply with this policy, and with its conflation of sex work and trafficking, the Government of Brazil publicly rejected an offer of some 40 million US\$ in HIV/AIDS funding, stating that sex workers were an integral part of Brazil’s HIV program, and that the government could not embrace a policy opposing its own constituents.<sup>72</sup> The prostitution pledge was subsequently the subject of two first amendment suits against the Bush administration.\*

How does human rights law and policy view this debate? The Palermo protocol asserts that “The consent of a victim of trafficking shall be irrelevant.” This is an important assertion, since both public health actors and sex worker advocacy groups have attempted to define voluntary or consenting participation in commercial sex as inherently different from coerced sex work. All sides of this sometimes contentious debate agree that trafficking is a crime and a rights violation, and there is broad global consensus that sexual exploitation of children is again both criminal and a rights violation. But while these distinctions are important, and have important health implications, from the perspective of trafficking in persons as a violation of human rights law the protocol is clear: even if a woman consents to be trafficked for sex work—it is exploitation which defines trafficking, not the consent of the victims.

A great deal more work needs to be done on the best practices for identification, treatment, and care of victims of trafficking. Their sexual health is clearly an important issue, but their psychological and emotional health needs are clearly vital as well.

## SPECIAL VULNERABILITIES— MSM AND OTHER SEXUAL MINORITIES

Homosexuality remains criminalized in over 80 member states of the United Nations, with punishments ranging from jail time to the death penalty (Fig. 111.4). And with the ongoing arrests and imprisonment of gay men and other MSM in Senegal, Nigeria, Cameroon, Iran, and, increasingly, Iraq, these laws continue to be enforced. MSM are at high risk for HIV infection in

\*One of the authors of this Chapter, CB, wrote a technical brief in support of the claimants for one of these cases.

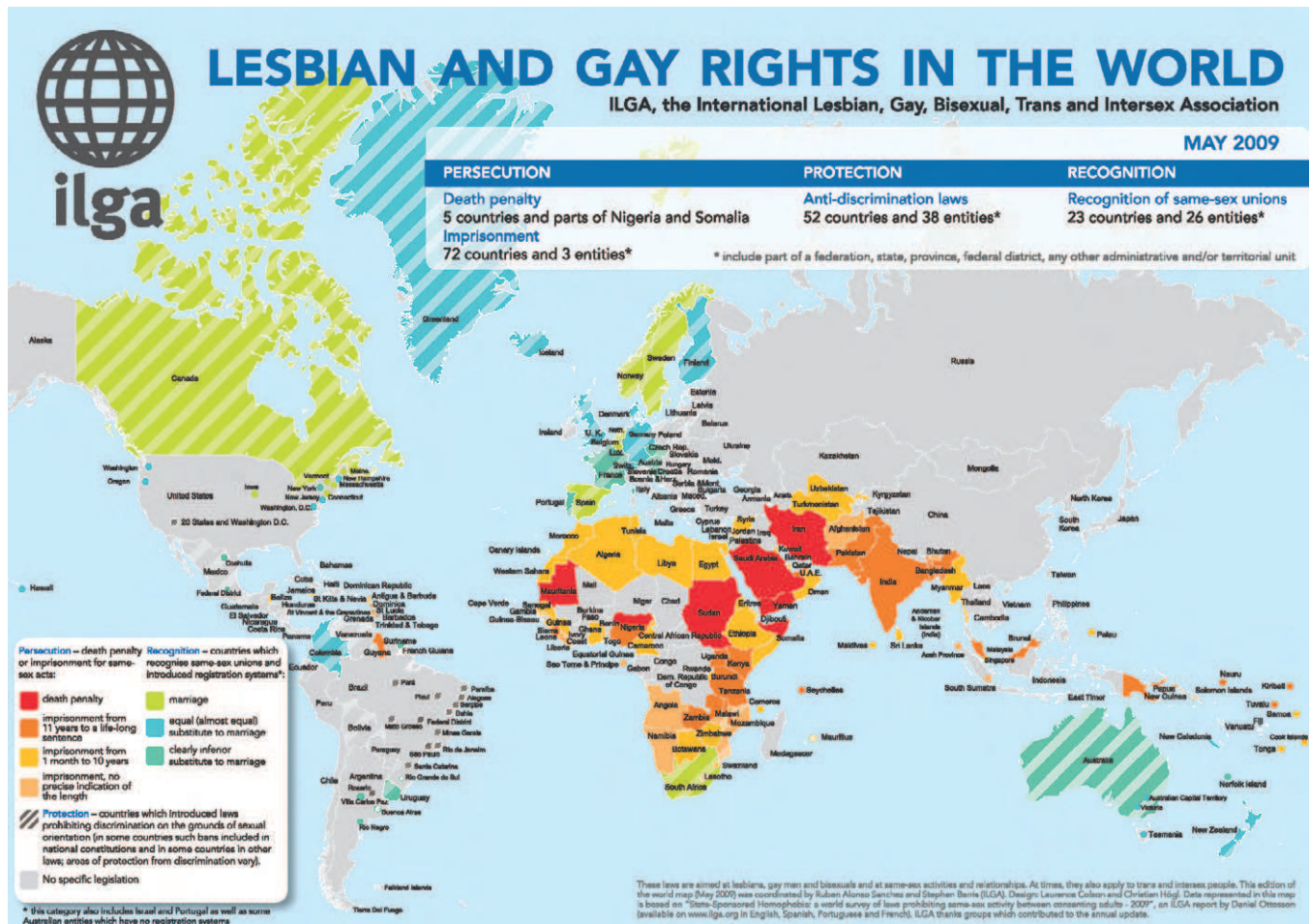


Fig. 111.4 Global summary of laws criminalizing same-sex practices as of May, 2009.

nearly every context where the virus has been described.<sup>74</sup> There are individual level risk factors for HIV and STI transmission including unprotected anal intercourse, or genital ulcerative diseases that likely transcend geography. However, higher order and more structural risk factors, such as criminalization, and other limits on human freedom and bodily integrity likely play roles in structural risks for HIV and STI as well.<sup>75</sup> Repressive legal contexts and pervasive social stigma can limit access for these men to appropriate STI and HIV services, including prevention, treatment, and care. And in such settings, healthcare workers may be part of the problem, as has been recently been demonstrated among MSM in three African countries, where MSM who disclosed their sexual orientation to healthcare workers were more likely to report having been blackmailed.<sup>76,77</sup> Stigma-targeting MSM and transgendered (TG) people can be extreme and can be life-threatening—as is currently the case with ongoing executions of gay men in Iraq and with violence and murders conducted with impunity throughout the world.<sup>78</sup> In these environments, even if there were funding for state-of-the-art comprehensive HIV prevention and care packages for MSM, they would likely be of limited value, since men in such settings are quite justified in not seeking care.

"In countries without laws to protect sex workers, drug users and men who have sex with men, only a fraction of the population has access to prevention. Conversely, in countries with legal protection and the protection of human rights for these people, many more have access to services. As a result, there are fewer infections, less demand for antiretroviral treatment and fewer deaths. Not only is it unethical not to protect these groups; it makes no sense from a health perspective. It hurts all of us."

*Ban Ki-moon, Secretary-General of the United Nations, August 2008.*

In many of these settings, criminalization of homosexuality has been coupled with ignorance of the risk for HIV infection and an almost complete lack of attention to oropharyngeal or anorectal STIs among gay men and other MSM. According to a review of the 2008 UNGASS reports on indicators of HIV among MSM, nearly half of those low and middle income countries that submitted reports did not have data on a single indicator of HIV rates or risk among MSM.<sup>79</sup> Yet, recent studies continue to characterize high burden of HIV and STIs, including HSV-2 infection, syphilis, and anal HPV among MSM in these same countries where the HIV epidemic was traditionally thought to be driven by high-risk heterosexual, vertical, and occasionally parenteral transmission.<sup>80</sup>



There is a powerful human rights argument for why anti-sodomy laws should be repealed; nearly all of the countries that criminalize homosexuality are signatories to the International Covenant on Civil and Political Rights which as of 1994 prohibits discrimination against sexual minorities.<sup>81</sup> And the International Covenant on Economic, Social, and Cultural Rights, also ratified by many of these countries, promises the highest attainable standard of health to all people, including sexual minorities.<sup>12</sup> The recent example of India overturning section 377 banning same-sex sexual practices in July of 2009, highlights the value in reminding these countries of their obligations to their citizens.<sup>82</sup> However, given different sociocultural norms, the human rights argument should be partnered with a public health argument; where stigma against homosexuality is both the rule of law and a sociocultural norm, it is nearly impossible to enact a comprehensive plan mitigating the harms of STI and HIV among MSM.

Our group recently completed the first assessment of human rights abuses for MSM in Malawi, Namibia, and Botswana; three countries which criminalize homosexuality. Human rights abuses among MSM in the study sample were prevalent across all three countries. Between 5% and 10% of the study participants, depending on the site, had been denied housing in the past for reasons other than the ability to pay. Being afraid to seek health services because of sexual orientation was reported by 17.6% (35/199) in Malawi, 18.3% (40/218) in Namibia, and 20.5% (24/117) in Botswana. While having been denied healthcare was less common with a pooled prevalence of 5.1% (27/533), disclosing sexual orientation to a healthcare worker was significantly associated with having been denied healthcare (OR 4.2, 95%CI 1.9–9.3). MSM reported being afraid to walk down streets in their own community most commonly in Botswana, but also to a lesser extent in Malawi and in Namibia ( $p < 0.05$ ). Overall 42.1% (222/527) of MSM answered yes to any of these markers of human rights violation. Of the total sample, 12.2% (65/533) indicated that they had been physically abused by a government or police official, with the highest rates in Namibia ( $p < 0.05$ ). Finally, 11.4% (61/534) of the sample reported ever having been raped by another man, with similar rates across the three sites. Blackmail or extortion on the basis of sexual orientation or behavior was quite prevalent in the sample with an overall rate of 21.2%. In the pooled analysis, univariate associations with blackmail included having either paid or received money or gifts for casual sex ( $p < 0.01$ ); having told a member of the family of one's sexual orientation ( $p < 0.01$ ); and having told a clinic or healthcare worker of one's sexual orientation ( $p < 0.05$ ), and not having had an HIV test in the preceding 6 months ( $p = 0.06$ ). Multivariate analysis was completed adjusting for these covariates and blackmail was significantly associated with having taken part in transactional sex (aOR 2.5, 95%CI 1.6–3.8), not having had an HIV test in the last

6 months (aOR 0.56, 95%CI 0.3–1.0), having disclosed same sex behavior to a member of the immediate or extended family (aOR 2.3, 95%CI 1.4–3.6), but not to healthcare workers (aOR 0.9, 95%CI 0.5–1.6).<sup>76</sup>

These structural barriers to available healthcare services will limit the efficacy of any interventions targeting individual level determinants of sexual infections among MSM and must arguably, be mitigated to effectively decrease HIV incidence and to treat curable STIs.<sup>25</sup> We would argue that the abolishment of anti-sodomy laws could serve to jump start a renewed, coordinated, and inclusive global HIV prevention effort where resources are allocated based on evidence-based need and not moral or religious principle. A roadmap for such an effort would consist of a multi-level approach addressing both individual and structural drivers of HIV and STI risk among MSM. And a comprehensive framework for addressing human rights standards for issues of sexual orientation and gender identity has recently been developed and termed the Yogyakarta Principles.<sup>83,84</sup> Moreover, in 2009 UNAIDS published an action framework providing a map for countries to adopt universal access for MSM and transgender people. In this document, the UN delineates leadership roles for the various UN agencies in this revived effort—with the UN development program (UNDP) being the global lead for matters of sexual diversity.<sup>85</sup> Now that these roles have been defined and a mandate delivered, it is time to move forward on protecting the rights and health of these men.

## Ways Forward

While the domains discussed here are diverse and the challenges faced by vulnerable populations in conflict, trafficking or repressive environments for migrant or sexual minorities differ markedly as well, several themes do emerge when exploring HIV and STIs within human rights frameworks. It is clear that sexual rights violations can and do impact vulnerability to sexual health threats, and that those who suffer from abrogation of sexual rights are at increased risk of disease acquisition, lack access to care, and face disproportionate burdens. It is also arguable that a focus on improving the rights context for vulnerable individual and groups has tangible health benefits—although here the evidence base is less strong. We would argue that human rights considerations need to be understood as social determinants of disease, and studied as such. This has the potential for benefit on several fronts—addressing the health needs of those most at risk, and attempting to mitigate the harms of rights abrogation in this most compelling of private domains. The field of sexual rights and health is in its infancy, yet the call for human dignity—for just treatment of those in conflict, in the misery of trafficking or the repression of discrimination based on gender and sexual orientation is one we cannot and should not ignore.



### Summary

Sexual rights violations can have profound impacts on the health and wellbeing of individuals and communities. A number of international rights conventions and treaties address sexual and reproductive health and rights, though biomedical research on the intersection of rights and sexually transmitted infections has been limited, largely to associations with HIV infection. Several domains have been identified as most relevant for understanding the impact of rights abrogation on STIs and HIV disease transmission and impact. These include HIV and STIs in conflict, in migration, in relation to sex trafficking, and the special vulnerabilities and rights abrogation-associated sexual minorities, especially men who have sex with men. There is an urgent need for greater recognition of the role of sexual rights violations as social determinants of disease, and for an expanded research agenda attempting to improve both the sexual health and human rights of those facing these inter-related challenges to well-being.

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## Introduction

Obviously, much of what we know or need to learn about infectious diseases cannot be obtained by the study of the infection in humans, particularly with respect to the basic mechanisms of pathogenesis, pathology, and the host response. Moreover, the complexities of a disease and interaction of the organism with its host cannot be modeled accurately *in vitro*; therefore, it is essential to have an animal model of the infection in order to gain these insights. Fortunately, there are a number of excellent animal models for several sexually transmitted infections; but as in most animal models, there are various advantages and disadvantages associated with each. In some cases, the actual etiologic agent of the human disease either is not infectious for animals or does not produce disease exactly as in the human; nevertheless most models, if used to answer appropriate questions, can and have provided valuable information. Indeed the critical factor is that a given model only be used to address a question for which it is most suited. In this chapter, we will present summaries of the various animal models for sexually transmitted infections and how each relates to or resembles the human disease and the nature of the host response to the infection; but we will also address those applications or research questions for which the models are likely to result in meaningful information.

## Chlamydial Infection

Chlamydia researchers have been fortunate in that there are three different animal models for genital infections, which allow for a range of research opportunities and the potential for comparison. Chlamydia are ubiquitous organisms infecting a variety of mammalian hosts and although in mammalian hosts other than human, the infection targets the gut, it has been possible to use the natural organism to infect genital sites. However, a caveat of chlamydial infections is that they tend to be very host-specific and attempts to infect smaller animals with *C. trachomatis* have met with varied success. A number of more detailed reviews of animal models for chlamydial genital tract infections have been published previously.<sup>1-5</sup>

## DESCRIPTION OF THE MODEL AND RELATIONSHIP TO HUMAN DISEASE

### Non-Human Primate

Not unexpectedly, infection of the non-human primate with chlamydiae most closely resembles human genital tract disease, and the model is made even more relevant by the ability to infect the animals with the human agent. Nevertheless, the non-human primate suffers the disadvantage of being prohibitively expensive and inconvenient for many basic research studies. Several different species of non-human primates have been infected in the female genital tract with *C. trachomatis*, including pig-tailed macaques (*Macaca nemestrina*),<sup>6,7</sup> grivet monkeys (*Chlorocebus aethiops*),<sup>8-10</sup> cynomolgus (*Macaca fascicularis*),<sup>11</sup> rhesus monkeys (*Macaca mulatta*),<sup>11</sup> marmosets (*Callithrix jacchus*),<sup>12</sup> and baboons (*Papio* sp.).<sup>13-14</sup> The only reported studies of infection of male non-human primates was a report of urethral infection of baboons by DiGiacomo et al.<sup>15</sup> and chimpanzees by Jacobs et al.<sup>16</sup>

The most commonly used non-human primate model is the pig-tailed macaque. Using serovar D, monkeys were inoculated in the cervix with  $10^6$  inclusion-forming units (IFU) and the course of the infection monitored.<sup>17</sup> The animals remained infected in the cervix for 6–15 weeks following a single inoculation, although infection of the fallopian tubes and tubal disease could not be demonstrated. Nevertheless, the observation of this rather lengthy lower genital tract infection appears to model human infection very well, which is also felt to be several weeks in length. This is in contrast to mice and guinea pigs in which the infection is much shorter at 3–4 weeks. Because it did not appear that cervical inoculation would result in ascending infection, Patton and colleagues inoculated serovars E and F directly into the fallopian tube and then monitored the infection at 1 week intervals by laparotomy with the collection of swabs and biopsies for histopathologic examination.<sup>6</sup> On days 7 and 14, marked edema and swelling of the fallopian tubes was observed, returning to normal size by day 35. In two of six animals, exudate was noted. Histopathologic examination showed initially a few



polymorphonuclear leukocytes in the mucosa and sub-mucosa at day 7 but progressed by day 14 and 21 to increased inflammation with lymphocytes (primarily T cells), plasma cells and mast cells. A similar response was reported in grivet monkeys as well.<sup>10</sup> Upon necropsy, there did not appear to be any evidence of scarring or tubal obstruction in the fallopian tube. Chlamydiae could be isolated for 1–2 weeks following inoculation; thus while the infection in the fallopian tube appears to be markedly shorter than in the cervix, the pathologic response does resemble very closely what has been observed in humans.<sup>18,19</sup>

Actual ascending infection to the fallopian tubes with *C. trachomatis* was demonstrated in pig-tail macaques after repeated cervical infection<sup>7</sup> and in grivet monkeys by a single inoculation through the cervical os.<sup>10</sup> While mild chronic salpingitis developed in 2 monkeys in the former study, one animal did develop peritubal and periadnexal scarring after reinfection with one fallopian tube becoming obstructed. These data demonstrated that ascending infection resulting in tubal obstruction could indeed be demonstrated in the non-human primate model, although repeated infections appear to be necessary; thus, the data from these two studies support observations in humans that infertility is more likely to occur following repeated infections. Histopathologic examination of the salpinx in both studies revealed numerous plasma cells and lymphocytes analogous to observations in women and suggestive that the etiology is associated with the adaptive immune response.<sup>7,20</sup>

An alternative non-human primate model has been developed in both cynomolgus and rhesus monkeys in which salpingeal tissue is removed from the animal and autografted into subcutaneous pockets on the anterior abdominal wall with as many as eight pockets in cynomolgus and 20 pockets in rhesus monkeys.<sup>11</sup> As a result of the graft, the oviductal tissue is able to retain its morphology and the individual pockets can be inoculated with chlamydiae. While the usefulness of this model is limited because of the subcutaneous nature of the graft, it has proven very useful to understand the histology of chlamydiae in actual fallopian tube tissue.

## Mouse Model

For the obvious reasons of lower cost and availability of a vast array of reagents and genetically manipulated animals, the mouse remains a very desirable animal to employ as a model for an infectious disease. Particularly with respect to the study of the host response, the mouse is by far the best model because of the available resources. With respect to chlamydial genital infections, female mice can be infected with *C. trachomatis* or the natural mouse chlamydia, *C. muridarum*. Both infections generally resolve in 3–4 weeks following intravaginal inoculation, considerably shorter than human infections. Furthermore, infection with *C. trachomatis* is mild and requires pretreatment of mice with Depo-Provera for infection to occur while *C. muridarum* can infect mice and produce a heavy infection in mice with or without Depo-Provera treatment, the hormone being primarily to stabilize

the estrous cycle of the mice in anestrus to facilitate infection, as mice cannot be infected during estrus.

Clearly, the advantage of infecting mice with *C. trachomatis* is that one is studying the actual human pathogen. Mice can be infected with all serovars of *C. trachomatis*; and interestingly, the course of the infection varies significantly based on the serovar used.<sup>21</sup> However, the major disadvantage of the model using human serovars is that pathology of the oviducts is very minimal following intravaginal inoculation, so the model's use is limited in the study of upper tract disease.<sup>22</sup>

*C. muridarum*, on the other hand, elicits a more aggressive infection and commonly causes ascending infection and long-term pathology in the oviduct, although the latter is dependent upon the strain of mouse used.<sup>22</sup> One can argue that *C. muridarum* is more relevant, particularly in the study of the host response because it is a natural parasite of the mouse. *C. muridarum*, the agent of mouse pneumonitis, was first isolated from the respiratory tract of mice<sup>23,24</sup> and was characterized as a model for genital infection by Barron and Rank.<sup>25,26</sup> There are two strains of *C. muridarum*, the Weiss strain and the Nigg strain. Both were isolated from mice at the University of Chicago, but a recent study has shown that they have distinct pathogenicity phenotypes with the Weiss strain being the more virulent of the two organisms.<sup>27</sup> The length of *C. muridarum* infection is also dependent upon the strain of mouse infected with C57 mice generally resolving the infection more quickly than Balb/c and C3H mice.<sup>22,28</sup> The pathologic response following chlamydial infection with *C. muridarum* has been well characterized in the mouse. Just as in the non-human primate, initially, there is a strong acute inflammatory response but within 7–10 days, a chronic inflammatory response consisting of CD4 and CD8 T cells and monocytes/macrophages appears which may persist at low levels for a period of time after the infection has resolved. The infection ascends the genital tract and causes scarring resulting in tubal obstruction and hydrosalpinx.

Virtually all of the studies on chlamydial genital infection in the mouse have been in the female; however, because the reproductive anatomy and physiology, especially with respect to the estrous cycle is completely different from the human, it probably is not the ideal model in which to study the pathologic response at the system level. Nevertheless, at the molecular and cellular level, the responses should be predicative for the human. Recently, infection of male mice has been demonstrated although this remains a difficult model because of the inability to monitor the infection sequentially in the same animal.<sup>29</sup>

## Guinea Pig Model

Analogous to the mouse, guinea pigs can be infected in the genital tract with a chlamydia native to guinea pigs. *Chlamydia caviae*, or the agent of guinea pig inclusion conjunctivitis, was originally isolated from the conjunctiva of young guinea pigs by Murray<sup>30</sup> and was found that it could also elicit a genital tract infection when inoculated intravaginally.<sup>31</sup> The infection resolves in 3–4

weeks, also shorter than human infections, and targets the exo- and endocervix but ascends the genital tract to the endometrium and oviducts in 80% of the animals.<sup>32</sup> The pathologic response, particularly in the oviducts is remarkably similar to the human. Just as in the non-human primate and the mouse, the initial host response is an acute inflammatory responses transitioning to a chronic inflammatory response, including CD4 and CD8 T cells, plasma cells, and monocytes/macrophages.<sup>32,33</sup> Of the animals that develop infection in the oviduct, only about 45% actually develop a pathologic response, but this may result in pyosalpinx followed by fibrosis, tubal obstruction, and hydrosalpinx.

An important advantage of the guinea pig is that the female has an estrous cycle of 17 days and very closely mimics the reproductive physiology and endocrinology of humans.<sup>34</sup> Infection in animals treated with estrogens and actual oral contraceptives is exacerbated with increased inflammation and incidence of upper tract disease<sup>35–37</sup>; thereby supporting studies in humans showing that women taking oral contraceptives have an increased incidence of chlamydial infection.<sup>38</sup>

Just as in humans, when pregnant guinea pigs are infected intravaginally, they are able to transmit the infection to the newborns at birth, resulting in inclusion conjunctivitis.<sup>31</sup> Unlike many other rodents, guinea pigs are fully haired and have their eyes open at birth. While it has not been demonstrated that newborn guinea pigs can develop pneumonitis at birth, typical chlamydial pneumonitis of the newborn has been produced by intranasal inoculation of 1 week old animals.<sup>39</sup> The pneumonitis is relatively mild but is very characteristic of chlamydial pneumonia in human neonates.

A major advantage of the guinea pig model is that male guinea pigs can be infected in the urethra and the course of infection can be monitored by urethral swabs.<sup>40,41</sup> Similar to the female guinea pig, the infection in the male resolves in about 3 weeks. The histopathology in the male urethra is also very similar to the female with an initial acute inflammatory response followed by a chronic inflammatory response. Ascending infection to the bladder has been documented in the immunologically intact animal, although it is uncommon. No evidence of infection of the seminal vesicles, prostate, vas deferens or epididymis has been found. However, if animals are immunosuppressed, a high incidence of cystitis can be observed as well as an occasional animal with organisms in the epididymis. Interestingly, both male and female guinea pigs can be infected intrarectally with the infection lasting 2–3 weeks.<sup>42</sup>

Perhaps the most significant aspect of the guinea pig model is that actual sexual transmission of chlamydiae from infected males to females can be reliably accomplished.<sup>43</sup> The females must be monitored to determine when they will enter estrous, and then males infected in the urethra are housed with the females about 6 days before the expected estrous. Infection of the female occurs in about 70% of the matings. It was particularly interesting that the course of cervical infection in the female inoculated sexually is significantly shorter than animals artificially infected with a comparable dose. It is tempting to speculate that chemokines

and cytokines in the semen may accelerate the host response in the female.

## HOST RESPONSE

Infection of each of the animal models generates a strong immune response and the animals develop immunity to reinfection, although the degree of immunity is dependent upon when after resolution of the infection the animals are challenged. In both the mouse and guinea pig, when challenged within 1 month after resolution of the infection, animals exhibit complete immunity, i.e., the animals do not become reinfected. However, when animals are challenged after a longer period of time, they do become reinfected, albeit the infection level is reduced and the course of the infection is abbreviated. When male and female guinea pigs infected with *C. caviae* were compared, the males maintained complete immunity for a longer period of time than did the females.

Vast majority of the immunologic studies have been performed in the mouse and guinea pig models. Each develops a substantial antibody response in both serum and genital secretions, with IgG dominating in both sites, although IgA is also elicited in the genital tract.<sup>45,46</sup> The IgG antibody develops concomitant with the resolution of the infection and remains at high titers for long periods of time in both serum and secretions, while IgA in secretions dissipates in about 50 days. The humoral immune response appears to be essential for both resolution of and resistance to infection in the guinea pig model<sup>47,48</sup>; however, antibody appears to be only important in immunity to challenge infection in the mouse.<sup>49</sup> It is not clear in humans how critical humoral immunity is.

In contrast to the humoral response, cell-mediated immunity is essential for both resolution of and resistance to chlamydial genital infection in both animal models.<sup>50</sup> Protective immunity associated with cell-mediated immunity is dependent upon a CD4 Th1 response which is consistent with data accrued in human studies.<sup>51,52</sup> While CD4 cells are essential for immunity to chlamydial genital infections, CD8 cells, although present, are not essential for immunity. The short-term nature of complete immunity appears to be dependent upon the presence of T cells in the genital tract.<sup>53</sup> Upon resolution of infection, T cells no longer localize in the genital tract, and animals again become susceptible to reinfection, albeit reinfection is shorter in duration and less intense.

## SUMMARY

There are three primary animal models used by researchers in the field of chlamydial research. While the non-human primate most closely resembles human disease, its use is limited by cost and availability. *C. trachomatis* is able to infect mice in the genital tract but the infection is generally relatively mild and the development of oviduct pathology is uncommon. The two best models for chlamydial genital infections, the mouse and guinea pig, employ agents which are host-specific and natural parasites

of each animal. The mouse infected with *C. muridarum* is ideal for the study of immune and pathologic mechanisms, while the pathogenesis and pathology associated with *C. caviae* infections appear to be more closely related to the human disease. Both can be used to evaluate potential vaccine candidates but primarily as proof-of-principle since *C. muridarum* and *C. caviae* only share genus-specific determinants with *C. trachomatis*. Infecting the mouse with *C. trachomatis* does provide the potential to test a human vaccine, but again, does not have the more severe pathologic sequelae of *C. muridarum*. Sexual transmission can only be accomplished in the guinea pig because of its similarity to humans in reproductive endocrinology.

## Gonorrhea

The development of an animal model to mimic human genital infection with *Neisseria gonorrhoeae* has been a difficult target, primarily because of the organism's unique specificity for the human host and the total lack of natural *Neisseria* species for rodents. In particular, the CD46 receptor required for pili-mediated attachment<sup>54</sup> and carcinoembryonic antigen<sup>55</sup> utilized for attachment by *Opa* proteins are not present in mice, nor can human transferrin or lactoferrin be utilized as sources of iron.<sup>56</sup> To some extent the lack of an optimal animal model has been compensated by the actual experimental inoculation of the urethra in human males.<sup>57</sup> While these experiments have yielded a significant amount of data, especially with respect to evaluating different mutant organisms and vaccine candidates, for obvious reasons, the entire course of infection, basic mechanisms of pathogenesis, and the host response cannot be studied in sufficient detail. Moreover, because of the potential for upper tract infection, female subjects cannot be studied so one cannot investigate factors specific to the female reproductive tract. A number of different animals have been tested for susceptibility to gonococcal infection<sup>58</sup> but only the non-human primate and mouse will be discussed below.

### DESCRIPTION OF THE MODEL AND RELATIONSHIP TO HUMAN DISEASE

#### Non-Human Primate

The only animal model in which urethral infection with gonococci could be induced, lasting 3–6 weeks, similar to humans, is the chimpanzee (*Pan troglodytes*). Male chimpanzees were inoculated in the urethra with either exudate from infected human males or approximately  $4 \times 10^7$  colony-forming units (CFU) of gonococci maintained by *in vitro* passage, contained in 2 ml of broth culture and the course of infection monitored by urethral swab.<sup>59,60</sup> Organisms could be detected from urethral swabs as early as 3 days after inoculation and were still detected 49 days after infection, after which the infection resolved. Clinical signs of urethritis, i.e., a slight discharge, were observed between 10 and 15 days after inoculation with *in vitro* cultured bacteria but in animals inoculated with exudate, the discharge lasted from days 4

to 30 and was quite prominent in the second week of infection. An exciting part of this model is the ability of *N. gonorrhoeae* to be transmitted from males to females.<sup>60</sup> The infected male chimpanzee was housed with a female and culture evidence of infection of the female by endocervical swab was obtained within 5 days. Organisms could be recovered as long as 39 days after exposure. There were no obvious clinical signs of infection in the female. While the chimpanzee would appear to be an excellent model for gonococcal infection, it is impractical to use because of expense and a limited supply of animals.

#### Mouse Model

There have been multiple attempts to produce a mouse model for genital infection with *N. gonorrhoeae*,<sup>61</sup> but until relatively recently, the results have been unsatisfactory. In general, in most attempts to model gonococcal genital infection in mice, the infections have been short-term and restricted to inoculation of mice during proestrous. Kita and colleagues were able to elicit a longer term infection in a particular strain of mice with endometrial cultures being positive for about 1 month<sup>62</sup>; however, these data were not able to be repeated in another laboratory using the same mouse strain.<sup>61</sup>

Because of the apparent restriction on susceptibility of infection to proestrous in mice, when estrogen levels are increasing as well as an apparent inhibitory effect of normal vaginal flora, Taylor-Robinson injected germ-free mice with 17- $\beta$ -estradiol prior to inoculation with  $2 \times 10^6$  gonococci.<sup>63</sup> As a result, they were able to culture gonococci from the vagina for up to 39 days. Organisms could also be detected in the endometrium and ovary. Nevertheless, no inflammation was observed.

In a modification of the model presented by Taylor-Robinson, Jerse inserted a 5 mg, 21 day controlled release pellet intradermally into Balb/c mice in the diestrous stage of their cycle, and at the same time, injected mice with an antibiotic cocktail consisting of streptomycin sulfate and vancomycin and added trimethoprim sulfate to their drinking water to reduce the normal vaginal flora.<sup>61</sup> Two days later, mice were inoculated intravaginally with *N. gonorrhoeae*. She evaluated inoculation with  $10^5$ – $4 \times 10^6$  CFU of three different strains. The length of the resulting infections varied according to the strain of gonococcus and the size of the inoculating dose, but ranged overall from 4.8 to 13.6 days. The infection course was generally over 12 days when  $10^6$  or more CFU were inoculated. The number of bacteria cultured from the vagina also varied greatly, ranging at peak levels from  $10^3$  to about  $4 \times 10^6$  CFU. Significantly, in this model, an acute inflammatory response could be detected in the vagina of the majority of infected mice, clearly indicating a pathologic response to the infection analogous to humans. It is also noteworthy that diplococci could be found associated with and within neutrophils, just as is classically observed in exudates from humans.

The regimen was later modified to use a water-soluble estradiol instead of the slow release pellet.<sup>64</sup> Similar results were observed in that the mice became infected, there was an infiltration of



PMNs, and the infection resolved concomitant to the loss of the estradiol effect.

Certainly, in humans gonococci may ascend the female genital tract and cause endometritis, salpingitis, and pelvic inflammatory disease (PID). When Jerse cultured endometrial tissue of animals infected intravaginally with *N. gonorrhoeae*, she did indeed isolate organisms but only in a low percentage of mice (17–20%) with a given strain of bacteria. No infection in the oviduct was reported. Nevertheless, the model does have the potential to model upper genital tract infection with gonococci.

Perhaps the most valuable aspect of this model is the ability to study the effect of the *in vivo* milieu on the genetic variation so characteristic of *N. gonorrhoeae*. While 99% of the organisms from two different strains were found to be piliated in culture, upon isolation from the mouse vagina with 48 hours of inoculation, the majority of the organisms had no pili, indicating that perhaps pili were not necessary for attachment in the mouse.<sup>61</sup> In contrast, the *Opa* protein, an important attachment protein with a high level of antigenic variation, is expressed on gonococci in the mouse genital tract. In fact, when mice were inoculated with a predominantly *Opa*-negative population, a high percentage of the isolates of several mice 14 days after infection were *Opa*-positive while the inoculum, passed for 5 days on artificial medium, did not express the *Opa* protein. These results paralleled observations in humans when *Opa*-negative organisms were inoculated in the male urethra and subsequent isolates were *Opa*-positive.<sup>65</sup> Similarly, just as in the human male model, isolates from individual mice did not necessarily express the same *Opa* protein, indicating a selection process in the mouse vagina. Selection for *Opa* proteins occurs in the mouse model in the absence of human carcinoembryonic antigen adhesion molecules, the major adhesion receptor for the *Opa* protein, and the recovery of *Opa*-positive variants from female mice is cyclical over time, which suggests the influence of reproductive hormones on *Opa* phenotype.<sup>66</sup> Overall, this model has proven to be valuable in examining basic host/bacteria interactions, including alternative mechanisms by which gonococci obtain iron in the mouse in the absence of transferring,<sup>67</sup> mechanisms by which gonococci resist killing by PMNs,<sup>68,69</sup> the role of lactate in *in vivo* survival,<sup>70</sup> and the evaluation of topical microbicides.<sup>71</sup>

## HOST RESPONSE

It is quite obvious in humans that a strong innate host response develops, but there is little evidence for the development of a protective immune response, as individuals can be infected multiple times. The host response to gonococcal infections has proven difficult to study because of the lack of a convenient model that truly mimics human infection. There is no doubt that an active innate response in the mouse develops upon infection, mainly as a result of the observed PMN influx to the local site. However, even though the infection in the mouse resolves, it is more likely that the resolution is dependent upon the loss of serum estradiol rather than the development of a protective

immune response.<sup>64</sup> When mice having recovered from a genital infection were reinoculated with the same strain, no difference was noted in the course of the infection from age-matched mice given a primary infection, supporting observations in humans.<sup>64</sup> It was also interesting in that there was only a transient IgG and IgA antibody response in vaginal washings and sera. Challenge infection did not show any evidence for an anamnestic antibody response. Therefore, there does not appear to be any substantial or sustained immune response to gonococcal infection in the mouse genital tract. While this may seem disappointing, the model, nevertheless, is reflective of the human situation.

That the mouse model can be used to evaluate potential vaccine candidates was demonstrated by Plante and colleagues.<sup>72</sup> They immunized mice intranasally with outer membrane preparations and then challenged the mice intravaginally. A reduction in the length of infection for the immunized mice indicated that a protective response had been elicited by the immunization regimen. An antibody response to several gonococcal antigens was observed in both serum and secretions.

## SUMMARY

The search for an instructive animal model for gonorrhea has been a difficult task, to a great extent, because of the unique specificity of the organism for its human host. While the chimpanzee appears to double for the human with respect to the specificity, there are the usual problems of expense and availability. The mouse model developed by Jerse is not perfect as well but does display many of the characteristics of human disease, i.e., development of an acute inflammatory response and lack of protective immunity or even a substantial adaptive immune response. Perhaps this model is best exploited to investigate mechanisms by which the organism evades or survives in the presence of an inflammatory response, mechanisms of antigenic variation, physiologic requirements of the organism *in vivo*, and the impact on the organism by the host physiology, which are areas already under investigation.

## Mycoplasma Genitalium Infection

*Mycoplasma genitalium* is a recently recognized sexually transmitted pathogen, first identified as a likely cause of inflammatory urogenital disease in men.<sup>73–75</sup> In the two decades since identification, *M. genitalium* has been implicated in several important female reproductive tract syndromes including endometritis, PID, cervicitis, and serologically with salpingitis and impaired fertility.<sup>76–80</sup> In men, *M. genitalium* is associated with non-gonococcal urethritis (NGU).<sup>75,81–84</sup> Overall, the data support but do not prove a causal role for ascending *M. genitalium* infections and the observed clinical outcomes.

Animal modeling of *M. genitalium* infections should help establish the causal relationships with both genital tract and joint infections as well as provide a means of testing novel vaccines and interventions. Unfortunately, the development of animal models has been hampered by the extremely fastidious nature of *M. genitalium* that makes confirmatory culture from human

and animal samples difficult.<sup>74,85–87</sup> For this reason, detection methods for *M. genitalium* are shifting to PCR quantification of the bacterial genome for diagnostic and research purposes. Using these enhanced detection methods and the successful modeling of other genital bacterial infections described in other sections of this chapter, several animal models for *M. genitalium* have been developed. Specifically, *M. genitalium* genital tract colonization has been achieved in non-human primate species and in hormonally conditioned mice as reviewed in several reports.<sup>88,89</sup> Finally, several genetically related *Mycoplasma* spp. have been used as surrogates of *M. genitalium* infection with successful genital tract infection of selected animal species.<sup>89–95</sup>

## DESCRIPTION OF THE MODEL AND RELATIONSHIP TO HUMAN DISEASE

### Non-Human Primates

As is the case for several other sexually transmitted pathogens, successful modeling of some of the aspects of *M. genitalium* infection has been achieved in both genders of selected non-human primates. Prior to experimentation, vaginal and urethral samples from each of the non-human primate species showed no evidence of natural infection by *M. genitalium*. Experimental infections of both male and female non-human primates were attempted by urethral or intravaginal application and in a subset of females by intraoviduct or transcervical administration of *M. genitalium*. The data are limited due to the associated costs and limits on available subjects for these species but collectively indicate that these species support varying levels of persistent colonization by *M. genitalium*, but they experienced minimal pathology. The pathologies that were observed model the inflammatory nature of this infection and suggest that *M. genitalium* likely contributes to infertility.

In the initial sets of studies, Taylor–Robinson and colleagues inoculated the urethra of male chimpanzees (*Pan troglodytes*)<sup>96</sup> with a culture adapted *M. genitalium* strain designated G-37 that was isolated from a male with a case of non-gonococcal urethritis.<sup>97</sup> In this first study, 4 young male chimpanzees were inoculated via the urethra and monitored for persistent colonization. Despite concerns regarding the clearing effects of urination, two of the animals developed infections as evidenced by persistent recovery of organisms from urethral swabs over 13 weeks of monitoring. A G-37 derivative was isolated from one of the animal's urethral samples and was used as a chimpanzee-adapted strain for subsequent studies. Subsequent animals were persistently colonized including at least 2 animals that were found to have blood-borne *M. genitalium* suggesting that systemic infections were possible.<sup>98</sup> Taylor–Robinson and colleagues also experimentally inoculated Rhesus macaques (*Macaca mulatta*) and found them to be “insusceptible.”<sup>88</sup> Cynomolgous monkeys (*Macaca fascicularis*) were found to be susceptible with 4 of 6 inoculated animals showing signs of colonization albeit with low levels of recovered organism in 2 animals.<sup>88</sup> In the other 2 animals

high numbers of organism ( $<10^7$  color-changing units (CCU)/mL) were isolated from urethral samples for up to 28 days.

Experimental infection of female animals also was evaluated in a number of non-human primate species. Specifically, female squirrel monkeys (*Saimiri sciureus*), tamarins (*Saguinus mystar*) marmosets (*Callithrix jacchus*), baboons (*Papio anubis*), and chimpanzees were colonized to some degree by *M. genitalium* following high titer inoculation.<sup>88</sup> Of the female non-human primates, vaginal inoculation of marmosets led to prolonged infection and inflammation of the genital tract. In an initial study, 6 female marmosets were inoculated vaginally with the G37 type strain and were followed for persistent infection and host response outcomes.<sup>97</sup> Vaginal swabs indicated 4/6 animals were actively infected and that *M. genitalium* persisted in the lower genital tract for up to 149 days similar to clinical case reports. Importantly, the 2 inoculated but uninfected animals and 2 mock-inoculated controls included in the study provided baselines for comparison to identify host responses and pathologies engendered by *M. genitalium*.

Female tamarins, squirrel monkeys, and chimpanzees also proved susceptible to colonization by *M. genitalium* following vaginal inoculation with high-titer stocks of the G37 type strain.<sup>88,98</sup> The authors concluded that these animals were colonized, albeit at low levels, using culture of vaginal swab specimens in specialized SP4 growth medium.<sup>75</sup> The fastidious nature of *M. genitalium*, the difficulties of axenic outgrowth from swab samples, and the use of PCR indicating high genomic burden in otherwise culture-negative samples likely indicates that these animals supported a more substantial level of infection than indicated by the SP4 outgrowth. Studies using PCR as an outcome measure have not been published.

Another aspect of clinical *M. genitalium* infection is ascension and damage to the upper reproductive tract. Of the non-human primates tested, squirrel monkeys and chimps both showed inflammatory outcomes in the lower genital tract but provided no evidence of natural ascension to the upper tract.<sup>88,98</sup> Intraoviduct administration is a commonly employed methodology to model infection of the upper tract when vaginal inoculation fails to create a natural ascension of the pathogen predicted by clinical observations. In a study designed to model upper tract infection, 3 female marmosets received G37 via intraoviduct inoculation during a laparotomy that produced endosalpingitis and lower genital tract colonization.<sup>88,99</sup> Intraoviduct inoculation also was performed in 2 grivet monkeys (*Cercopithecus aethiops*) where, like marmosets, salpingitis was produced but, in this case, no obvious lower tract colonization was observed. Of the non-human primates tested, squirrel monkeys and chimps both showed inflammatory outcomes in the lower genital tract but provided no evidence of ascension to the upper tract or the more serious pathologies.<sup>88,99</sup> Finally, to better model natural infection, 3 female baboons (*Papio anubis*) were inoculated with *M. genitalium* across the cervix and followed for lower tract colonization and upper tract disease. Two of the 3 animals had persistent vaginal colonization and two developed pelvic inflammation.<sup>88</sup>

Collectively, the studies in non-human primates established that *M. genitalium* was capable of infecting lower and upper genital tract tissues but the extreme costs associated with development and maintenance of the primate animal models prohibited larger scale studies to address biological variability as part of an effective model of reproductive tract infection.

## Mouse Model

Smaller animal models have been evaluated over the last two decades to address the non-human primate short-comings and to provide opportunities to evaluate therapies and interventions including novel vaccines and antibiotics. Although other small animals were evaluated, mice seem to offer the greatest potential. Initial experiments by Furr and Taylor–Robinson provided evidence that *M. genitalium*, strain G-37, could establish experimental genital tract infections in female mice,<sup>95</sup> but, to date, no evidence of infection of male mice has been published. There are several closely related *Mycoplasma* spp. that have been used as surrogates for modeling of *M. genitalium* genital tract infection, including *M. pneumoniae*, *M. pulmonis*, and *M. fermentans*. In fact, in a single reported male mouse study with *M. pulmonis*, an interesting phenomenon was observed in many of the inoculated animals in three of six tested inbred lines of mice.<sup>100</sup> At periods of time distant from inoculation, inoculated male mice experienced prolonged priapism that lasted in one case 44 weeks. In fact the authors noted “erections that persisted, apparently continuously, for up to 44 weeks can certainly be described as priapism, although so remarkable is the phenomenon in duration that it would seem to deserve a different term to reflect this aspect.”<sup>100</sup> This condition has anecdotal correlates in clinical literature and may be related to hypercoagulation associated with *M. pneumoniae* infection.<sup>101</sup>

For female animals, experimental infection by *M. pneumoniae*, *M. pulmonis*, and *M. fermentans* required hormonal conditioning to enhance susceptibility to infections.<sup>88,92,95,102</sup> Synchronization of the estrous cycle offered additional advantages for subsequent evaluations including pathology development and fertility issues. Importantly, by increasing susceptibility, hormonal conditioning reduced the numbers of animals required per group. Capitalizing on the successful modeling of other STI pathogens, including those detailed in this chapter, and using related *Mycoplasma* spp. as surrogates, Taylor–Robinson and colleagues tested the susceptibility of hormonally conditioned inbred mice to *M. genitalium* infection. Their preliminary studies showed that progesterone conditioned but not estradiol benzoate-treated BALB/c mice were susceptible to vaginal *M. genitalium* infection.<sup>88</sup> This was consistent with susceptibility to the surrogates *M. pneumoniae* and *M. pulmonis* but was distinct from estrogen-based susceptibility to the genital pathogen, *M. fermentans*, that only colonized estrogen-conditioned mice.<sup>95,102</sup> Unfortunately, there was no evidence of ascended infection or upper tract pathology in the progesterone-conditioned animals.<sup>88,95</sup>

In the decades following these initial studies, the quality and formulations of both progesterone and estradiol were improved

and now include long-acting versions that are utilized for a number of STI animal models. Utilizing longer acting Depo formulations of both progesterone and estrogen, a recent set of studies showed a differential infection pattern but indicated both conditions allowed for persistent vaginal colonization.<sup>103</sup> For these studies, several inbred lines and the commonly used, outbred Swiss Webster mice were found to be susceptible following two injections of either estradiol cypionate (0.25 mg; Depo-estradiol, Pfizer) or medroxyprogesterone acetate (3 mg; Sicor, CA) at 7 and 1 day prior to *M. genitalium* inoculation. A high-titer inoculation ( $2 \times 10^7$  CCU) was vaginally delivered for the G-37 type strain and a low passage, contemporary isolate designated M2300<sup>104</sup> after extensive washing and resuspension in sterile PBS. After this inoculation, *M. genitalium* reproducibly colonized both the lower and upper reproductive tract tissues persistently. Infected animals shed viable organisms from the vaginal cavity for several months with vaginal titers maintained at low levels (average of  $5 \times 10^4$  genomes/swab). These more recent studies also utilized PCR-based assays<sup>87</sup> to evaluate tissues and swabs from inoculated animals. Vaginal shedding was intermittent with an average of 50% of the collected swabs being PCR-positive at each sampling time.<sup>103</sup>

Using the more sensitive PCR-detection approach, it was possible to identify preferred sites of colonization in the upper tract of the mouse as a predictor of the sites infected in humans. Based on both PCR and viable organism outgrowth, an interesting outcome of the two tested hormonal conditions was the differential ascension of the infection into the upper tract and possibly systemic dissemination of the bacteria.<sup>103</sup> Animals conditioned with estradiol cypionate were more often found to have upper tract colonization and had a higher frequency of hydrosalpinx development.<sup>103</sup> Specifically, estrogen-dominated animals infected with either G-37 or M2300 had detectable *M. genitalium* in the uterine horns at 3 days host infection, in the oviducts by 7 days post-infection and in knees on day 10 post infection. Such data suggest a causal role for *M. genitalium* in cases of infertility. Interestingly, by PCR, *M. genitalium* also was detected in the knee joints of infected mice providing evidence that *M. genitalium* may disseminate from the vagina to colonize synovial sites offering a potential model of reactive arthritis. Finally, the hormone-dependent susceptibility to *M. genitalium* is compatible with other bacterial STI models allowing for the potential to model co-infections as described later in the chapter.

## HOST RESPONSE

Human infection leads to a directed antibody response<sup>74,105–107</sup> but there is little to no information regarding cell-mediated immunity at present. In females a pronounced antibody response to the major adhesin protein, MgPa, has shown<sup>105,108,109</sup> some cross-reactivity with other *Mycoplasma* spp.<sup>107</sup> Clinically, the associated conditions suggest there is a strong inflammatory component to the host response that has been modeled in human cell cultures<sup>110,111</sup> and is beginning to be evaluated in animal models.



Male non-human primates that were infected via the urethra, showed a transient urethral response that included increased numbers of polymorphonuclear leukocytes that was absent after the animals were treated successfully with antibiotics.<sup>96</sup> The infected animals also showed significant increases in serum antibody to *M. genitalium* proteins. One of two chimpanzees with resolved infection was challenged 6 months after antibiotic treatment but was not infected suggesting that it was immunologically protected.<sup>96</sup> Female chimpanzees also developed increased numbers of polymorphonuclear leukocytes in vaginal samples following infection with subsequent increases in antibody titers to *M. genitalium*.<sup>88</sup> In subsequent studies with infected chimpanzee sera, Morrison–Plummer and colleagues showed that a selected set of immunodominant epitopes were common to the chimp antibodies and to infected humans.<sup>107</sup>

Studies in the mouse suggest similar host responses to those reported in humans and in the limited primate studies. The lower cost and availability of mice allowed for several studies to be completed to address potential cross protection by respiratory infection with *M. pneumoniae* to subsequent vaginal infection by *M. genitalium*.<sup>112</sup> These studies showed that respiratory infection by *M. pneumoniae* protected mice against vaginal challenge with the same organism<sup>95</sup> but not against vaginal challenge with *M. genitalium*.<sup>112</sup> In more recent studies, infected mouse sera were tested on lysates of *M. genitalium* by immunoblot.<sup>103</sup> Proteins bound by the mouse antibodies were then characterized by MALDI-TOF/TOF mass spectrometry confirming that MgPa also was observed to be an immunodominant protein in outbred mice. Additional proteins recognized by the mouse sera included *M. genitalium* EF-Tu, DnaK (Hsp70) and the E1  $\alpha$  subunit of pyruvate dehydrogenase.<sup>103</sup> Interestingly, each of these proteins is considered a putative component of the cytoskeleton in *M. pneumoniae*<sup>46</sup> suggesting that they should be evaluated for function in *M. genitalium* replication, human infection and as novel targets for clinical diagnostics.

Finally, the mouse has provided some insights into the initial responses to infection that may be chronically elicited contributing to the clinical pathologies associated with *M. genitalium* infections.<sup>113</sup> In recent studies, human genital tract and macrophage cell cultures elicited proinflammatory responses when they were exposed to live or dead *M. genitalium* or fractionated or recombinant *M. genitalium* proteins.<sup>110</sup> The utility of the mouse model should allow a systematic evaluation of the cytokines and chemokines elaborated from infected vaginae as well as cell-mediated immune responses in genital and possibly joint tissues. Importantly, direct, causal associations with inflammatory disease and its impact on fertility could be explored in the mouse model.

## SUMMARY

The recent identification of *M. genitalium* as a genital tract pathogen that is transmitted sexually has created an active field of research that includes the creation of useful animal models. The research has been aided by the success with other STI pathogen modeling as well as success with closely related *Mycoplasma* spp. Unlike other bacterial

STI with similarly narrow host range, the non-human primate studies suggest that *M. genitalium* may not create the same pathologies in female animals reducing the utility of these extremely costly and limited species. Early success with mouse modeling led to recent interest and improvements utilizing different formulations of both estrogen and progesterone. The resulting mouse vaginal challenge model that showed several inbred lines, including C57Bl/6 and a common outbred mouse strain were susceptible to persistent colonization and upper tract infection should allow future studies of vaccines and interventions. The limited host response data suggest that mouse and man have similar immunodominance hierarchies. The mouse also offers an opportunity to address basic pathology questions including the role of *M. genitalium* in fertility. Finally, because mice could be made susceptible to infection following either estrogen or progesterone conditioning, co-infections with other STIs may be modeled in the mouse.

## Syphilis

Of all the sexually transmitted infections, research on syphilis has probably been carried out for the longest period of time. *Treponema pallidum* has been an exceptionally difficult organism to work with because of the simple reason that it cannot be cultured *in vitro* and requires inoculation into rabbit testes for production of sufficient organisms for experimentation. Unlike chlamydial and gonorrheal infections which gain access to the lumen of genital tract via fluid transfer, *T. pallidum* enters the body via microabrasions of the skin or mucosal epithelium leading to local replication and subsequent dissemination to the draining lymph nodes and peripheral circulation, so that the resulting disease is systemic rather than a local mucosal infection. Thus, in modeling syphilis, it is not critical that infection be initiated in the reproductive tract of males or females, but rather it should be able to demonstrate local dermal infection followed by systemic spread. Initially, there was a great deal of difficulty in producing an effective animal model until it was recognized that the key factors in infecting animals were the strain of *Treponema* used and the size of the inoculating dose, generally at least 10<sup>7</sup> organisms.<sup>114</sup> Virtually, all of the animal studies since the 1950s have utilized the Nichols strain, originally isolated from human cerebrospinal fluid (CSF) in 1912.<sup>115</sup> The primary model used for syphilis research is the rabbit although the guinea pig has also proven to be an useful model. For a brief period, some studies were initiated with the Syrian hamster but this model has not been used in recent years.<sup>116</sup> Some studies have also been published using non-human primates.<sup>117</sup> The early studies on animal models for syphilis are extensively reviewed by Turner and Hollander.<sup>114</sup>

## DESCRIPTION OF THE MODEL AND RELATIONSHIP TO HUMAN DISEASE

### Rabbit Model

The most commonly used and arguably an indispensable animal for research on syphilis is the rabbit because of the necessity to

grow *T. pallidum* in rabbit testes to produce organisms for all aspects of treponemal research. Generally, New Zealand white rabbits are used, although care must be taken to determine if there is any serologic evidence for infection with *Treponema paraluis-cuniculi*, a naturally occurring treponemal infection of rabbits.<sup>118</sup> Male rabbits are routinely injected in each testicle with 1 mL of  $2\text{--}4 \times 10^7$  spirochetes. In 7–11 days after orchitis has developed, animals are euthanized and the organisms are extracted from the testes.<sup>119</sup> Yields can be increased by injections of cortisone acetate following infection.

In order to characterize the pathogenesis of testicular infection, male rabbits were injected with  $2\text{--}10 \times 10^7$  organisms in each testicle and were euthanized at various times after infection to evaluate the early stage of infection.<sup>120</sup> Inflammation of the testes was apparent by 6–8 days after infection and the testes were enlarged and somewhat hemorrhagic. The peak level of orchitis occurred between 8 and 13 days after infection, doubling in size with diffuse swelling and firmness, and then returning to normal size by 31 days after infection. Microscopically, there was an obvious interstitial lymphocytic infiltration by day 6, increasing to peak levels by days 10–13 with the majority of the cells identified as T cells and only a few B cells. Subsequently, the cellular content began to decrease with an increase in interstitial fibrosis and apparent cure. Treponemes were first detected by fluorescent-labeled antibodies at day 3 and continued to multiply through day 13. The number of organisms decreased dramatically following the peak T-cell response and could not be detected by immunofluorescence by day 17 and thereafter. Nevertheless, while there appears to be local resolution of the infection, organisms may persist in the lymph nodes and perhaps blood for 3–4 years in a period of latency.<sup>114</sup>

Similar to testicular injection, inoculation of  $2 \times 10^7$  spirochetes intradermally results initially in erythema and induration at the site of infection by days 3–4, reaching maximum size of 16 mm by 2 weeks after infection.<sup>121</sup> Central ulceration then develops with resolution of the lesion by day 36. In this particular study, spirochetes could be detected up to 2 weeks after infection but disappeared by 4 weeks. However, at 6 weeks, organisms could be found in the testes, spleen, and lymph nodes, indicating systemic dissemination. Earlier studies demonstrated that *T. pallidum* rapidly disseminates systemically and persists for the lifetime of the animal.<sup>114</sup> The histopathologic response in the dermis was also similar to the response in the testes. Initially, a slight perivascular and diffuse infiltration of the dermis and subepidermal tissues with mononuclear cells developed, the majority of which were T cells. The mononuclear inflammatory response continued to increase by 2 weeks with extensive lymphocytic infiltration surrounding the hair follicles, and then declined by 4 weeks, concomitant with the disappearance of organisms. Thus, the dermal response to *T. pallidum* in the rabbit is remarkably similar to the primary lesion in human syphilis.

Obviously, syphilis is a complex disease with pathologic considerations extending beyond the dermis and early stage disease. One of the major aspects of late syphilis is the invasion

of the CSF and the development of neurosyphilis. Marra and colleagues were able to use the rabbit to model early infection of the central nervous system.<sup>122</sup> Rabbits were inoculated intracisternally with  $1.5\text{--}5.1 \times 10^7$  spirochetes. Serologic evidence (VDRL) for infection was in 86% of the animals by 2 weeks and in all animals by 4 weeks after inoculation. When the CSF was evaluated, mononuclear pleocytosis could be seen by 2 weeks after infection, increasing to peak levels by 9 weeks and persisting as long as 20 weeks; however, the response was not consistent with 50% of the animals having  $>10$  white blood cells/ $\mu\text{L}$  at 6 and 9 weeks after inoculation. Similarly, viable treponemes could only be demonstrated in the CSF and/or brains of 66% of the animals at 6 weeks after infection, but the presence of organisms did correlate with the peak mean serum VDRL titer and CSF pleocytosis.

Another key aspect of syphilitic disease is the transplacental transfer of organisms to the fetus, resulting in congenital syphilis. In order to model congenital syphilis, Fitzgerald inoculated pregnant animals intravenously at various times of gestation with varying doses of bacteria ranging from  $4 \times 10^8\text{--}4 \times 10^9$ .<sup>123</sup> In contrast to rabbits inoculated with killed organisms which had an 8% rate of stillborn, infected does had a 28–42% rate of stillborn offspring. Interestingly, only one of the offspring showed evidence for birth defects, and there did not appear to be any long-term developmental effects on the surviving animals. As evidence that organisms did indeed pass the placental barrier, viable organisms were indeed detected in extracts from fetuses from an interrupted pregnancy. Moreover, organisms were detected in the spleen of an offspring one week after birth.

## Guinea Pig Model

While not as susceptible to infection with *T. pallidum* as the rabbit, the guinea pig, nevertheless, has been used as a model for syphilis and can be infected intradermally, subcutaneously or intratesticularly with the intradermal route being the most effective and appropriate to model the disease.<sup>124</sup> Just as in the rabbit, the Nichols strain of *T. pallidum* is the most effective strain at eliciting disease, and the size of the inoculating dose is also critical in establishing infection. In addition, male guinea pigs and younger guinea pigs appear to be more susceptible to infection.<sup>124</sup>

When injected in the testes, guinea pigs do not develop orchitis to the same degree as rabbits, although spirochetes could be isolated from the testes and inguinal lymph nodes up to 6 months after infection. Intradermal inoculation produces lesions similar to the rabbit with an initial erythematous area 1–2 weeks after inoculation, progressing from a small papule to definite induration, finally becoming necrotic with ulceration.<sup>124–</sup>

<sup>126</sup> Organisms can be demonstrated by dark field examination in the lesions. In about 10% of the animals in one study, secondary lesions developed several weeks after resolution of the primary lesion.<sup>126</sup> Systemic spread and long-term persistence of the organism in the spleen and various lymph nodes was observed, just as in the rabbit.

Upon histopathologic examination of dermal lesions, a marked lymphocytic, histiocytic, and PMN infiltration was elicited and numerous treponemes could be detected.<sup>124</sup> In the lymph nodes, hyperplastic and hypertrophic changes in the germinal centers were observed reaching a maximum 6 weeks after infection but still apparent 18 months after infection.<sup>125</sup>

## HOST RESPONSE

In both rabbit and guinea pig models of syphilis, the lack of immunologic reagents has inhibited the detailed description of the host response that one can obtain in mouse models. However, with newer molecular techniques and the availability of rabbit and guinea genome sequences, the ability to assess a wider range of immunological parameters is becoming available.

The host response in both animal models, particularly in the rabbit, bears a great deal of resemblance to the human. In rabbits, there is no doubt but that a strong immune response develops following testicular infection resulting in resolution of the local infection even though organisms continue to persist in lymph nodes in a latent infection.<sup>120</sup> Evidence for immunity to intradermal infection challenge was apparent as early as 25 days after infection and was still present 73–80 days after infection.<sup>120</sup> In guinea pigs as well, the infection resolves but lymph nodes remain positive for as long as 6 months.<sup>124</sup> It is still not clear how the organism can persist in the lymphoid tissue in the presence of such an active immune response. Both rabbits and guinea pigs respond with both humoral and cell-mediated responses. Both produce antibody detectable by the FTA-ABS assay, but interestingly, antibodies to the cardiolipin antigen as measured by the VDRL or RPR assays, which develop in humans and rabbits<sup>127</sup> are not elicited in the guinea pig.<sup>126,128</sup> The presence of a profound T cell and mononuclear response is apparent upon histopathologic examination and is likely the key disease-causing mechanism.<sup>121,129</sup>

The appearance of T cells at the local site corresponds with the disappearance of treponemes from the lesion, suggesting that the cell-mediated immune response may be playing a role in the resolution of infection.<sup>129</sup> Analysis of the proliferative response of rabbit T cells to treponemal antigens was quite pronounced as well.<sup>119</sup> When the cellular constituency of the lesions was assessed by flow cytometry, the initial response shows a preponderance of CD4 T cells but CD8 T cells gradually entered the site as well.<sup>130</sup> Not surprisingly, the response was characterized as a Th1 response. Unfortunately, it has not been possible in the rabbit to establish the exact role of cell-mediated immunity in the protective response. However, adoptive transfer studies were performed in the guinea pig model. Pavia and Niederbuhl transferred immune splenic and lymph node cells into guinea pigs and then challenged the animals intradermally.<sup>131</sup> The resulting lesions in animals receiving immune cells were smaller in diameter and resolved more quickly than in guinea pigs receiving normal cells, and the numbers of treponemes in the lymph nodes were reduced. T-cell-enriched cells also demonstrated a protective response as did a B-cell-enriched population but to a somewhat lesser extent.

Interestingly, the passive transfer of immune serum to rabbits was also able to delay the development of lesions and reduce the lesion size.<sup>132,133</sup> In guinea pigs, the transfer of antibody reduced the number of animals developing lesions, as well as the number of organisms in the lymph nodes.<sup>134</sup> Thus, the data would suggest protective roles for both antibody and cell-mediated immunity, although clearly more work needs to be done to establish the exact mechanisms.

## SUMMARY

Clearly, the rabbit has been a valuable model for the study of syphilis and is able to model different aspects of the disease. Aside from the current lack of immunologic reagents, research with this model is impeded by the lack of inbred rabbit strains. Importantly, the reliance of the model on a single strain of *T. pallidum* makes it difficult to determine the impact of different variants on disease. The fact that other strains are not as infectious for the rabbit, indicate that there are most likely genetic modifications in the organism which affect virulence. The guinea pig has provided additional research opportunities, especially with respect to the study of the host response, but the current unavailability of inbred guinea pigs makes further experiments problematic as well.

## Herpes Simplex Virus Infection

Since the first description of a creeping virus now known as herpes simplex virus (HSV), a tremendous amount of research has been completed including the establishment of a number of extremely well characterized and successful animal models. Many aspects of the human infection have been effectively modeled in several animal species as reviewed in detail by others.<sup>135–140</sup> This section of the chapter will briefly cover modeling in non-human primates and will highlight the success with the two more commonly used animal species, mouse and guinea pig and finally will describe the potential utility of a cotton rat model of genital HSV-2 infection. Although not discussed here, there are a limited number of reports of modeling atypical HSV-2 disease including ocular infection<sup>141,142</sup> and skin disease.<sup>143</sup> In a small number of reports, studies of interventions, preventatives or vaccines were completed in multiple species, often with the goal of satisfying the “two animal rule” prior to clinical trial evaluations. Such studies provide the opportunity to validate the utility of each animal model as well as identify distinctions that could confound decisions for compound prioritization. It is reasonable to note that the promiscuous nature of HSV allows this virus to infect a variety of species and most all cell cultures studied. As such, recent research to prioritize promising interventions and vaccines is being completed in enhanced human cell culture systems prior to evaluation in animal models. Such cell culture studies subscribe the three R's of animal research (refine, reduce, replace) but do not adequately substitute for compound evaluation in the context of interacting immune and epithelial target cell systems.



## DESCRIPTION OF THE MODEL AND RELATIONSHIP TO HUMAN DISEASE

### Non-Human Primate

Limited studies have been completed with HSV-2 in non-human primates in part due to the success with the smaller animal models that offer greater availability and lower costs. A single report of genital challenge with HSV-2 in owl monkeys (*Aotus trivirgatus*) indicated that animals, immunized with mixtures of HSV-1 and HSV-2 glycoproteins, were not protected against genital HSV-2 challenge.<sup>144</sup> These animals displayed symptomatology similar to human disease but were not extensively followed for recurrent disease or shedding of reactivated virus. A separate study that examined HSV-2 infection in adolescent and adult female Cebus monkeys (*Cebus albifrons*) indicated that vaginal inoculation of a laboratory strain created a mild, self-resolving primary disease that effectively modeled human infections.<sup>145</sup> All of the 16 adolescent animals and 19 of 21 adults developed clinical disease signs and shed virus over a 3-week period. The other two adults remained resistant to subsequent challenges. The report indicated that only three episodes of recurrent lesions were observed in the infected animals with more showing sub-clinical shedding following vaginal sampling. The authors concluded that the adolescent animals were more susceptible to latent infection using the outcome measures available at that time.<sup>145</sup> An evaluation of the host immune response in these animals suggested they effectively modeled the human response to infection as will be discussed below.

### Mouse Model

In general, mice are highly resistant to intravaginal HSV challenge and, as is the case for other STI, can only be consistently infected through hormonal conditioning with progesterone.<sup>138</sup> Most commonly, animals are conditioned with one or two injections of Depo-Provera beginning roughly 1 week prior to viral challenge.<sup>136,138,140</sup> The challenge dose utilizes  $\sim 10^4$  plaque forming units of clinical or laboratory strains of HSV-2 delivered vaginally after the epithelium is swabbed to remove debris and potentially create microabrasions to serve as portals of entry. This approach consistently led to a lethal infection in >95% of test animals. Given the availability of mice, it has been possible to examine viral kinetics in tissues along the path of infection in the host that is not possible in humans. After inoculation, HSV-2 replicates in the genital tract followed by rapid (<2 days) movement to the peripheral nervous system via sensory nerves. Unfortunately, in mice the infection progresses to the central nervous system; and without intervention, a fatal encephalitis results in nearly all of the infected mice. This is in distinct contrast to the human infection that rarely causes lethal outcomes following genital infection and is a primary disadvantage of the mouse model. The model does provide a very predictable disease course that occurs in all tested outbred and inbred strains of mice. Within 2–3 days of primary inoculation, mice experience hair loss and

erythema near the vaginal os but show minimal skin lesions. As the infection advances loss of bladder control can lead to chronic urine release with fatal outcomes by 7–15 days post-inoculation. In animals that survive the primary infection by vaccination or by antiviral intervention, the virus establishes latency in sacral ganglia but the animals do not show spontaneous recurrent skin lesions nor do they shed reactivated virus.<sup>140,146</sup>

Although the mouse model of genital HSV infection does not ideally mimic human disease, it provides several advantages that make it an excellent small animal system for study of vaccines to protect against lethal outcomes. The mouse model has been used widely to evaluate host immune responses as discussed below.<sup>136,147</sup> The mouse also provides distinct advantages for testing of topical and systemic interventions and preventative compounds including: (i) a mucosal route of viral challenge, thus the agent's ability to interfere with infection at the portal of entry can be evaluated; (ii) both clinical (incidence of signs and mortality) and virologic (isolation of virus from the genital tract) endpoints for evaluating efficacy can be assessed easily; (iii) there are abundant reagents to test both innate and acquired immune responses, and (iv) a disease course that is relatively rapid and therefore inexpensive.

The study of topical preventatives, referred to as microbicides, has made wide use of the mouse model to prioritize the compounds in the pipeline. Plant-based humanized antibodies,<sup>148</sup> natural products,<sup>149</sup> and synthetic TLR agonists<sup>150–153</sup> as preventatives for genital HSV-2 have all been evaluated in the mouse model. A recent approach tested in the mouse capitalized on siRNA technology and the expression of such molecules in the vaginal epithelium that models many aspects of the human tissue.<sup>154</sup> This study showed a durable protection due to the virally delivered siRNA that interfered with HSV-2 infection.<sup>154</sup> Importantly, the mouse model also has been used for safety testing of topical compounds that in some cases created a paradoxical increase in susceptibility.<sup>155</sup> In such studies a variety of methods have been established to assess the impact of the topical applicant upon the integrity of the vaginal epithelium including imaging (colposcopy), innate immune responses (cytokine elaboration into the vaginal cavity), and susceptibility to reduced challenge doses of HSV.<sup>155</sup> Collectively, studies of these topical compounds delivered directly to the vaginal mucosa in the mouse have identified the most promising compounds for study in other animal models and clinical trials.

With the advent of genetically modified animal lines, the mouse model also has provided a system to evaluate the role of host genes on HSV-2 pathogenesis.<sup>156–165</sup> This work has been advanced quickly by the abundance of transgenic and genetic knock-out mouse strains. As an example of this use of the mouse model, work by Spear and colleagues has identified several alternate cellular receptors that are involved in genital tract infection.<sup>164</sup> Using HSV-2 infection of specific knock-out mice, several routes of cellular entry of genital epithelia have been identified helping direct development of novel preventatives designed to block receptor binding.<sup>164</sup> Specifically, the absence

of the primary HVEM or secondary nectin host proteins alone did not prevent genital tract infection. Double knock-out mice were found to have virtually undetectable levels of infection of the genital epithelium. These studies necessarily need to be validated as there are indications that some mouse proteins do not provide consistent mimics for human protein interactions with the virus.<sup>166</sup> This approach also has been successful in dissecting the role of the immune response<sup>147</sup> through elimination of an aspect of the acquired<sup>159,161,165,167–169</sup> or innate<sup>157,158,170–172</sup> immune responses.

HSV-2 infection of pregnant women poses additional threats and can lead to serious complications for the neonate. Asymptomatic shedding during pregnancy has been associated with preterm delivery, lower birth weight and, importantly, a severe and often fatal infection of the neonate as it passes through infected tissues.<sup>173,174</sup> The pregnant mouse has been utilized to model this aspect of human genital herpetic disease with some success.<sup>175–177</sup> The majority of animals experimentally infected during pregnancy experienced varying levels of fetal impact that correlated with the timing of challenge relative to day of gestation. Animals infected early in gestation showed frequent spontaneous abortion of the litter while those infected later in gestation experienced difficulties with delivery of healthy pups.<sup>175</sup> Interestingly, among the studies in pregnant mice, there was some discord in the approach to enhancing susceptibility with a suggestion that pregnant mice did not require progesterone conditioning if they were swabbed effectively in advance of vaginal application of HSV-2.<sup>175</sup>

The need to hormonally condition mice prior to infection has provided some insights into the interaction of the virus with the genital epithelium but does not correlate with susceptibility in the humans. There are now several reports suggesting multiple mechanisms that explain why progesterone conditioning creates a more susceptible environment for vaginal HSV-2 infection.<sup>178–180</sup> It is clear that progesterone dominance thins the vaginal epithelium and shifts the immune system into a more “suppressed” state.<sup>181–183</sup> Using ovariectomized mice treated with saline, estrogen or progesterone or a combination of both hormones, Gillgrass and colleagues established that estrogen provided resistance to the tested challenge doses and the progesterone/estrogen-treated animals showed focal infection that slowly advanced relative to progesterone alone.<sup>181</sup> Since those studies, additional work has suggested that estrogen dominance is associated with enhanced immune response to vaccines<sup>184,185</sup> and provides for better activation of genital-associated lymphoid tissues.<sup>182</sup> The role of hormonal-conditioned susceptibility remains a concern for STI modeling in the mouse in general and continues to be a focus of research.

Recently, STI research has utilized the “humanized” mouse as a system for testing the behavior of human pathogens and vaccines in a small animal system manipulated to support reconstitution with human immune system components. Consistency of reconstitution is a concern in these animals but they are argued to provide an effective preclinical system to test compounds prior

to clinical trial. They are being used as a small animal model for HIV-1 infection as discussed later in the chapter. Humanized mice are created using immunodeficient animals generated through radiation exposure or by genetic alteration that then are implanted with CD34+ stem cells isolated from human umbilical cords. Many of these animals develop functional immune cell populations that are able to be educated to recognize specific antigens and to model proper expression of selected cytokines. In a recent study, humanized mice were immunized against HSV-2 and then challenged.<sup>186</sup> The animals were given Depo-Provera and were followed for viral titer through vaginal washes as well as immunologic outcomes including human antibody titer, evaluation of immune cell types present in the vaginal cavity and T-cell proliferation assays.<sup>186</sup> The results suggest that this model may provide an improved preclinical system for STI vaccine evaluation but still fails to address the lethal outcomes associated with HSV-2 infection in mice making therapeutic vaccine and reactivation and recurrent disease evaluations impossible. These aspects of genital herpetic disease are better modeled in the guinea pig.

## Guinea Pig

Genital HSV-2 infection in guinea pigs is remarkably similar to genital herpes in humans and offers several advantages over the mouse model effectively covered in several reviews.<sup>139,140,187–190</sup> Disadvantages to this animal system include limited immunological reagents, incomplete sequence for the guinea pig genome and added costs and labor associated with the care and use of the larger animal. It is of note that additional immunological reagents are being generated for study of the guinea pig making this animal more attractive for future studies. For HSV challenge, inoculation is performed via a natural route (intravaginal or intraurethral) with either serotype and results in a vesiculo-ulcerative genital skin disease that can be quantified using a lesion-score scale.<sup>188</sup> Zosteriform skin disease associated with rectal and/or genital infection also has been effectively modeled in the guinea pig following dermal inoculation.<sup>143</sup>

The pathogenesis of infection in the guinea pig has been well characterized and involves HSV-2 replication in the genital tract followed by spread via sensory nerves to neurons in the sacral root ganglia. The animal engenders immune responses that limit acute infection with resolution of genital lesions by day 14 post-inoculation. The primary infection is rarely lethal and does not require hormonal conditioning of the female animals. Latent infection is established in the sensory neurons that innervate the genital tract followed by periodic reactivation that produces spontaneous recurrent lesions that can be scored daily.<sup>187,188</sup> Quantification of the latent viral DNA burden in the ganglia also provides an opportunity to assess prophylactic approaches to protect the naïve host. Recurrent lesions can be experimentally induced through UV exposure of the anogenital region of infected animals<sup>191–194</sup> and, as reported recently, through stress associated with overnight fasting.<sup>195</sup> Such induced recurrent

disease offers great opportunity for studying therapeutic regimen including vaccines,<sup>144,190,194,196–198</sup> immunomodulators,<sup>152,193,195,199</sup> and antivirals.<sup>200,201</sup>

Perhaps most importantly, the guinea pig effectively models asymptomatic shedding that is believed to be a major means of transmission to the naïve human host. Cervicovaginal swabs can be collected and assessed for HSV-2 through quantitative PCR that allows evaluation of impact upon both frequency and magnitude of shedding.<sup>152,195,197,198</sup> Using this outcome, therapeutic measures designed to reduce vaginal viral titers to reduce the likelihood of transmission can be evaluated. Specifically, viral shedding frequency is based on reactivation in the ganglia while the magnitude of the shedding event likely reflects viral replication at the vaginal mucosa. This system has shown successful therapeutic immunization of latently infected animals with a glycoprotein vaccine that experienced both reduced recurrent disease and sub-clinical viral shedding.<sup>202</sup> Collectively, studies in the guinea pig have shown that immunization does not prevent infection, but can prevent or at least significantly reduce both the primary disease and subsequent recurrences, the latter observation being correlated with a reduction in the burden of the latent virus.<sup>203</sup>

Similar to the mouse model, the guinea pig also has provided insight into the vertical transmission of HSV-2 to neonates.<sup>137,204</sup> In these studies, newborn guinea pigs were inoculated intranasally and followed for disease signs on the skin, eye, and mouth as well as neurological signs indicating infection of the central nervous system common to human neonatal disease.<sup>137</sup> Respiratory infections were common in this model as were disseminated skin infections that responded well to acyclovir therapy.<sup>137</sup> Interestingly, in survivors, spontaneous cutaneous lesions developed indicating recurrence at primary infection sites that were self limited and appeared as effective models of the human infection. In a follow-up study, the age of the newborn and alternate infection routes were evaluated to better model the exposure that occurs during passage through an infected birth canal.<sup>204</sup> The work concluded that the age of the animal was inversely proportional to the onset, severity, and extent of primary disease as well as the duration of recurrent disease. Animals that were inoculated on the skin of the scalp showed the best outcomes while intranasal infections led to the most severe disease states that without intervention were most often fatal<sup>204</sup> effectively modeling the human condition. Subsequent studies, utilizing intranasal inoculation of newborns, tested the impact of acyclovir therapy and/or passive antibody delivery.<sup>205</sup> The results indicated that combination therapy protected the newborns from fatal infection and significantly reduced the duration of skin, eye, and respiratory disease signs and suggested improved courses of therapy for human newborns.

### Cotton Rat

In a single report, the cotton rat (*Sigmodon hispidus*) has been described as an animal model for genital HSV-2.<sup>206</sup> Like the guinea pig, the cotton rat does not require hormonal preconditioning to enhance susceptibility and experience primary disease similar to

humans following vaginal inoculation. The primary lesions resolve followed by limited spontaneous recurrent lesions. Interestingly, Yim and colleagues reported that HSV-2 DNA could be detected in several disseminated tissues including liver, kidney, lungs, and brain that suggest a systemic infection not necessarily observed in humans. Recurrences could be induced by treatment with dexamethasone allowing for therapeutic compound and vaccine studies as indicated above for the guinea pig.<sup>206</sup> Although only reported in a single study, the data from the cotton rat suggest it may be an additional small animal model to study prophylactic and therapeutic intervention strategies for genital herpes.

### HOST RESPONSE

Each of the described animal models has been evaluated for innate, humoral and cell-mediated immunity responses to HSV genital infection. In many cases, the findings directed subsequent human studies and supported the development of therapeutic strategies as noted above. The most substantial data set has been generated in the mouse system where successful characterization of innate, humoral, and cell-mediated immune responses has been completed. Using genetically altered or depleted of selected immune cell populations established that antibody alone was insufficient to protect against vaginal challenge<sup>158,161,163,165,167</sup> and that a variety of cell types played key roles in the resolution of HSV-2 infections.<sup>147,162,168–170</sup> The data clearly indicate a very complicated immune response with contributions from both antibody and cell-based clearance of virus.

With regard to innate immune responses, the identification of toll-like receptors (TLR) directed additional studies in TLR knock-out mice. Such animals have been utilized to examine the recognition of HSV-2 and subsequent innate immune responses and the impact on pathogenesis. TLR2<sup>-/-</sup> mice, infected with HSV-1, suggested a role for TLR2 but not TLR4 in the innate response to herpetic infection. Paradoxically, TLR2<sup>-/-</sup> mice experienced less neuropathology to HSV-1 CNS infection that was explained by a noted reduction in cytokine elaboration and inflammatory outcomes.<sup>172</sup> These and other studies established a role for TLR2 and 9 in HSV-2 responses and led to a number of human clinical correlates of note. Specifically, polymorphisms in selected TLR genes including TLR2 were associated with increased lesion and shedding behavior in infected humans.<sup>207</sup> Clearly, additional research is needed in animal models and in clinical trials to dissect the steps in the initial recognition and response to HSV-2 infection that ultimately condition acquired responses that should impact both establishment of latent infection and subsequent reactivation in the peripheral and central nervous systems.

In the mouse and guinea pig, studies of neural immune responses to HSV-2 have clearly established that there are resident B and T cells in the ganglia where rounds of latency and reactivation occur.<sup>208,209</sup> These studies effectively changed the understanding of immunity in the nervous system that was believed to be devoid of typical immune cell function. Completion



of these types of studies help to refine vaccine development including vaccines designed to be used therapeutically in order to address the latent sites of infection that serve as a reservoir for transmission.

## SUMMARY

HSV genital infections are prevalent in the adult population and are of increasing concern given the association to acquisition of other STIs including HIV-1. Research in animal models has provided much of our understanding of pathobiology of infection as well as refining strategies for prevention and therapeutic interventions. The mouse model offers many advantages including access to essential immune reagents to study responses and vaccine potential. Disadvantages include genetic distinctions in the way that HSV proteins interact with the mouse proteome relative to the human proteome<sup>166,210</sup> and the lethal outcomes associated with HSV-2 vaginal infections in mice. HSV researchers have made great use of the guinea pig model that addresses many of the major disadvantages with the mouse model. In this fashion the combined use of the mouse and guinea pig has provided for the effective use of available immunological reagents for the mouse where the guinea pig options are limited. The need to follow disease resolution and subsequent recurrent lesion development is then addressed with subsequent studies in the guinea pig. As an indication of this paradigm, the guinea pig model was predictive of the efficacy of acyclovir<sup>211</sup> and has been used to evaluate a number of prophylactic vaccine strategies.<sup>212</sup> In addition, it was used to prove the concept of immunotherapy, i.e., the use of therapeutic vaccines to control recurrent disease<sup>213</sup>; an approach extended subsequently to humans through a clinical trial.<sup>214</sup> Finally, guinea pigs that are infected also shed virus from the vaginal cavity at high frequency and in the absence of clinical disease signs. This aspect of the human disease is critical to the study given the role of viral shedding in HSV-2 transmission. The naïve sex partner is unaware of the infected partner's status due to a lack of disease signs despite shedding of significant amounts of virus.<sup>215,216</sup> Together these two main animal models have provided substantial information and have advanced successful approaches to begin to reduce transmission of this important STI.

## HIV Infection

HIV-1 is one of the most difficult STI pathogens to model because of the extremely limited host range of its virus family. The only non-human species that has proven to be susceptible is the chimpanzee. HIV is a member of the lentivirus genus that includes a number of genetically similar viruses with equally limited host ranges.<sup>217,218</sup> Of the identified viruses, several, with varying levels of genetic similarity to HIV-1, provide opportunities for surrogate animal modeling that represent some of the most common and well-characterized systems for research. Although lentiviruses have been isolated from a variety of animal species (see Stump and VandeWoude for review<sup>219</sup>) currently, none have been isolated from a rodent limiting the options for HIV studies

to larger animal models. Over the last decade, two approaches have been initiated to expand the options for HIV modeling in animals. The first involves the production of chimeric viruses that maintain tropism for the animals they were isolated from but have genetic replacements that direct expression of selected HIV genes to enhance study of vaccines and antivirals.<sup>217,220</sup> The second approach is the genetic alteration or xenografting of rodents to enhance their susceptibility to HIV.<sup>221–224</sup> Given these enhancements, there has been a great deal of success on modeling aspects of HIV infection in a limited number of animals as reviewed in detail by others.<sup>219,220,225</sup> The next few pages will highlight the most commonly employed models using HIV surrogate viruses, chimeric viruses, and finally altered rodents. Finally, outside the scope of this section, there are a number of effective pathogenesis models utilizing non-lentiviruses that produce similar disease as reviewed in detail.<sup>219</sup>

## DESCRIPTION OF THE MODEL AND RELATIONSHIP TO HUMAN DISEASE

### Non-Human Primate Model

Initial studies, just over 2 decades ago, established that the chimpanzee (*Pan troglodytes*) is susceptible to HIV infection.<sup>226</sup> This was a likely outcome given the belief that HIV-1 infection of humans resulted from direct interactions with chimpanzee.<sup>227</sup> Following intravenous delivery, inoculated animals developed persistent viremia but did not develop obvious pathology.<sup>226</sup> Vaginal installation of HIV-1 also led to a persistent viremia in a small number of chimpanzees but again did not cause immunodeficiency.<sup>228</sup> Genital inoculation of pigtail macaques (*Macaca spp.*) created a transient infection that also did not produce disease.<sup>229</sup> A slightly better success rate was established by inoculating “animal-adapted” HIV-2 in pigtail macaques and baboons (*Papio anubis*) that resulted in a reduction in CD4+ cell counts and subsequent AIDS.<sup>229</sup> Unfortunately, in each case the lack of reproducible HIV-1 infection of these costly animals and the minimal or undetectable disease created by the infection led researchers to seek more viable alternatives.

The discovery of simian immunodeficiency viruses (SIVs) substantially advanced the ability to model the pathogenic process associated with HIV-1 infection in humans. SIVs are found commonly in a number of African monkey species and are believed to be close relatives to HIV-1.<sup>219</sup> Interestingly, the African monkey isolates were found to be highly infectious and pathogenic for Asian macaque monkeys (*Macaca mulatta*, *M. fascicularis*, *M. nemestrina*) that developed more pronounced clinical signs similar to human HIV-1 infection.<sup>230</sup> SIV was originally isolated from rhesus macaque (*Macaca mulatta*) monkeys (SIVmac) and was associated with an AIDS-like illness.<sup>231–233</sup> Since the original isolation, SIV strains have been isolated from several animal species including chimpanzees (SIVcpz), sooty mangabeys (SIVsmm), African green monkeys (SIVagm), and mandrill (SIVmnd).<sup>217</sup> Molecular clones have been generated for many of these strains

and have been analyzed for pathogenesis in selected non-human primates.<sup>234,235</sup> As is the case for most of the lentiviruses, extreme limitations in host range were observed for each but several of the SIVmac clones were able to elicit “AIDS-like disease” in Asian rhesus macaques.<sup>231,235</sup>

Of the SIV isolates, the majority of animal modeling of HIV-1 has been accomplished with SIVmac inoculated experimentally into male and female rhesus macaques.<sup>236</sup> SIV has been transmitted experimentally by vaginal inoculation creating a disease state in the infected animals that was similar to that created by intravenous administration of the cell-free virus.<sup>237,238</sup> Subsequent studies with a single vaginal inoculation showed high infection rates as evidenced by persistent viremia independent of the timing of inoculation relative to menstruation.<sup>239</sup> Marx and colleagues did report that progesterone implants enhanced vaginal infection with SIV suggesting vaginal epithelial thickness may impact susceptibility.<sup>240</sup> This finding coincides with clinical observations that women are more susceptible to HIV-1 infections during pregnancy and the associated high levels of progesterone.<sup>241</sup> The model was used to show proof of concept through formalin fixed virus immunization that protected a high percentage of animals from infections.<sup>242</sup> Male macaques also proved susceptible to SIV inoculation through urethral infusion or inoculation of the penile foreskin.<sup>238,243</sup> Limited indications of sexual transmission of an experimental SIV infection also have been reported in pigtail macaques. The infected females that mated with naïve males apparently transmitted the infection but other routes (biting, cleaning, etc) were not excluded.<sup>244</sup> Importantly, SIVmac also models aspects of HIV infection of the gut and nervous systems.<sup>245–249</sup> The SIV/macaque model system provided insight into HIV-1 vertical transmission and transmission via breast milk.<sup>238,250–252</sup> Finally, as a model of rectal transmission, male rhesus and pigtail macaques were successfully infected by intrarectal installation of cell-free virus leading to a persistent viremia.<sup>253,254</sup>

Although a substantial step forward, the SIVmac model lacked the capability to fully address the unique accessory functions encoded by HIV-1 and the pathology elicited in experimentally infected macaques was not sufficient to fully model all aspects of the human disease. In addition, SIVmac clones share 30–50% genetic identity with HIV-1 with substantial dissimilarity localized to the envelope glycoprotein impacting the value of modeling of antibody responses and vaccine evaluations. To address some of the shortcomings, molecular chimeras of SIV and HIV (designated SHIV) were created and utilized in several non-human primate species.<sup>217</sup> A subset of the chimeras, that express the HIV glycoprotein and accessory genes, retains the ability to infect the original non-human primate species but better model the HIV-1 life cycle and human infection. Several genetic approaches were taken but the most successful also included serial passage through either cultured monkey cells or macaques.<sup>255</sup> Such SHIV isolates are now the mainstay for use in animal models where mucosally inoculated macaques develop persistent viremia, experience a loss of CD4 cells and subsequently develop the SIVmac AIDS-like

disease.<sup>256–259</sup> The success with this challenge model has made this system the most frequently employed to evaluate HIV-1 vaccine candidates. With addition of the HIV-1 reverse transcriptase into successful chimera the system also has been used to evaluate antiviral regimen and emergence of drug resistance.<sup>260,261</sup> This model system also has provided important information about the production of envelope-neutralizing antibodies<sup>262</sup> and the potential for passive immunization methods to alter pathogenic outcomes of SHIV infection.<sup>263,264</sup>

In general, the SIV or SHIV infections of mucosal surfaces results in an acute viremia and depletion of CD4 cells albeit under distinct timelines. For SHIV, CD4+ T-cell depletion occurs within weeks of inoculation leading to AIDS in a few weeks to 2 years in this animal model; this does not effectively model human HIV-1 infection and subsequent AIDS development (~10 years).<sup>265</sup> Further, study of the less successful chimera helped identify several macaque proteins that provided levels of resistance to SHIV providing important insights to the failings in the human host response to HIV-1.<sup>217</sup> This and other issues pushed the development of the next generation of SHIV chimeras that essentially start with HIV-1 and introduce necessary genetic elements to support infection of and replication in monkey cells. Several such chimera have been reported in the last few years that are ~90% HIV-1 but have the necessary SIV elements to overcome the host restrictions at least in cell cultures of macaque cells.<sup>266–268</sup> In a recent *in vivo* study, one of the next generation SHIV successfully infected 4 pigtail macaques creating a viremia that declined over time and did not cause the depletion of CD4+ cells.<sup>269</sup> These promising approaches will require additional work but show great promise to further enhance the utility of this animal model system.

## Feline Model

Another member of the lentivirus genus, feline immunodeficiency virus (FIV), was identified in domestic cats that presented with immunodeficiencies (leukopenia) and other disease signs.<sup>270</sup> Unfortunately, at a genetic level, FIV is more similar to ungulate lentiviruses than those isolated from primates.<sup>271</sup> Unlike SIV, FIV is naturally T-cell tropic and provides the opportunity to better model the interactions between this lentivirus and the T-cell target. FIV infects both CD4+ and CD8+ T cells.<sup>272</sup> Importantly, FIV infects target cells through interactions with the CXCR4 entry receptor and the CD134/OX40L binding moiety that are primarily expressed on CD4+ T cells.<sup>273,274</sup> As such the binding and entry of FIV are similar to HIV-1 as are some aspects of the transmission process including vertical transmission to kittens during gestation and suckling.<sup>275–277</sup> In adult animals, FIV is primarily transmitted through biting or cleaning behaviors but has been experimentally delivered via transfusion of infected blood.<sup>278</sup> Interestingly, although FIV can be isolated from a variety of non-domestic felines, only domestic cats show clinical signs consistent with HIV-1 infections.<sup>278</sup>

Infected cats experience a prolonged acute phase viremia and clinical signs including lymphadenopathy, anorexia, gingivitis, cachexia, and an increased susceptibility to opportunistic infections.<sup>278</sup> In infected cats, the CD4:CD8 ratio declines, similar to HIV-1 infected humans and, over time, a CD8 rebound is reported and FIV-specific antibody titers increase.<sup>279</sup> Experimentally infected cats also show low T-cell levels at mucosal surfaces and are highly susceptible to subsequent challenge with a variety of opportunistic pathogens. Domestic cats have been infected by a number of routes including most mucosal surfaces. Considering the female animal and a model of sexual transmission, 10 of 11 cats were infected by vaginal inoculation with a relatively high dose of FIV.<sup>280</sup> This report also documented that a leading microbicide at the time, Nonoxynol 9 (N9), could be applied to cats prior to inoculation to protect them from infection.<sup>280</sup> Isolates from each of three FIV clades, A, B and C, have all established experimental infections in domestic cats.<sup>279,281</sup> In 2002, a clinical license was granted for a vaccine against FIV in domesticated cats and has been used to support the likelihood of successful vaccine development for other lentiviruses.<sup>282</sup>

Although useful for specific studies, a major disadvantage to this HIV surrogate animal model system is the dramatic differences in the feline reproductive system relative to human females. The anatomy of the cat's genital tract is substantially different from the human with a cornified vaginal epithelium that changes substantially during the estrus cycle of the animal.<sup>135</sup> This may have contributed to the success of the N9 trial that was found to enhance susceptibility due to vaginal epithelial damage.<sup>283–285</sup> Another concern for the model is the availability of pathogen-free cats. Despite these disadvantages, there are a number of directed uses for the system including screening of topical antivirals and vaccine evaluation. Finally, the neurotropism of and neuropathology associated with FIV make it a useful model system to study those aspects of HIV-1 infection in humans.<sup>286–288</sup>

## Transgenic Rat Model

As noted previously, rodents have not proven susceptible to lentiviral infection and as such have not been useful model systems. To enhance the potential for these more convenient, smaller animals, transgenic technology has been employed to create Sprague–Dawley rats that express human CD4 and CCR5 that serve as the main receptors for HIV infection of T cells. The initial animals were engineered to express both human proteins selectively on CD4 T cells, macrophage, and selected neural tissue cells that represent main target cell types for HIV-1 infection.<sup>289</sup> This initial model allowed for persistent harboring of HIV-1 after systemic challenge and allowed for an efficacy study of an entry inhibitor<sup>290</sup> but failed to generate a prolonged viremic state showing low but detectable serum levels of virus.<sup>289</sup> Interestingly, these studies identified that the model allowed for substantial entry of virus but most of the transgenic target cells were not supportive of early HIV-1 gene expression.<sup>290,291</sup> Similar to the

work noted above in macaques, use of this animal model allowed the identification of another rat protein as a inhibitor of HIV-1 replication. Specifically, a critical role for cyclin T1 (CycT1) in the elongation steps of HIV-1 transcripts was identified and was a major impediment for implementation of the transgenic rat system.<sup>222</sup> To overcome this limitation, additional genetic material was introduced to the existing transgenic rat such that cell-specific expression of human CycT1 was accomplished.<sup>222</sup> Although the transgenic expression of CycT1-boosted HIV-1 gene expression sustained viremia and pathologies were not observed indicating that additional work will be required to make this system a fully useful animal model for HIV-1 infection. Interestingly, similar work is being pursued in transgenic mice with extremely different outcomes.<sup>292</sup>

## Humanized Mouse Model

The pioneering work of several groups of researchers established a number of mouse models that capitalized upon animals that were genetically deficient in key aspects of the immune system. As such, these CB-17 severe combined immunodeficient (SCID)<sup>293</sup> mouse lines stably accept immune system reconstitution by xenografting of human cells or tissues. SCID mice lack B and T-cell function but retain much of the innate immune response including natural killer (NK) cells. Several derivatives have been created that have enhanced the ability to create more useful humanized mice as will be discussed below.<sup>294</sup> Based on the human xenografting, varying degrees of HIV-1 target and response cell production is created earning these manipulated animals the moniker “humanized mice.”<sup>295–297</sup> These animals are being used widely for HIV-1 modeling as well as a number of other difficult to model human pathogens. Recent and thorough reviews by Denton and Garcia or Hoang and colleagues provide detailed and extensive overviews of the successes and failures with these models.<sup>223,224</sup> In the next few paragraphs the highlights of each of the three main mouse systems will be covered in the context of HIV-1 infection and response.

The original humanized mice utilized SCID animals that were injected intraperitoneally with peripheral blood lymphocytes (PBL) that provided a transient presence of human immune cells including B and T cells.<sup>297,298</sup> As an alternative, the non-obese diabetic SCID mouse (NOD/SCID) with reduced NK cell function also has been utilized because it is more supportive of engraftment.<sup>299</sup> Injection of human PBL in either SCID or NOD/SCID mice produced a transient (weeks) presence of mature human T and B cells that quickly waned<sup>300,301</sup> due to a lack of progenitor cells. The mature cells were most often in circulation making some natural routes of infection less reliable (e.g., vaginal). One group reported a better success rate with vaginal inoculation of SCID-hu PBL mice following progesterone conditioning.<sup>302</sup> This severe limitation allowed proof of concept and limited studies of viral cytopathic effects and vaccines but did not allow for accurate modeling of human response to HIV-1 infection. The presence of B cells in the system was exploited for



several vaccine evaluations.<sup>303–306</sup> The advantage of this system is that the mouse can receive PBL from individuals that have been vaccinated to evaluate the potential of specific vaccines. At the very least, SCID-hu mice provided a first susceptible mouse model for HIV-1 infection<sup>302,307</sup> supporting further refinements in HIV-1 humanized mouse models.

To create a longer-lived engraftment, human fetal liver and thymus tissues were implanted in the kidney of SCID animals (SCID-hu Thy/Liv) to create a hybrid organ that provided a renewable source of immune cells. The SCID-hu Thy/Liv model originally was created to allow for modeling of human hematolymphoid cell differentiation<sup>296,308,309</sup> but provided improved options for HIV-1 infection modeling. Histologically, the hybrid organ established proper architecture for the thymus and was found to be vascularized and viable over time. The tissue allowed for prolonged production of immune cells (months) that unfortunately were released into systemic circulation at extremely low levels. In fact, most of the human cells were localized to the Thy/Liv tissue graft reducing options for HIV-1 inoculation routes and requiring direct injection of HIV-1 into the graft. Interestingly, the tissue produced expected cell populations including CD4, CD8, and a variety of other T-cell populations that were tolerant to the mouse “self antigens,” indicating an education function.<sup>310,311</sup> Unfortunately, few human B cells, macrophage and dendritic cells could be detected. Additionally, the sequestering of the human immune cells precluded study of natural routes of HIV-1 infection (e.g., genital tract) and limited the utility of the model for vaccine or other intervention evaluations. The system was useful for assessing antivirals<sup>312</sup> and the impact of genetic alterations in HIV-1 to evaluate the role of selected genes.<sup>313–316</sup>

In the 20 years since the first humanized mice, the models have been further refined using progeny generated from subsequent crosses with more substantial immunodeficits. The other lines include recombinase activating gene (Rag2<sup>-/-</sup>) knock-out mice and interleukin receptor gamma chain (ILg<sup>c</sup>-/-) knock outs.<sup>294</sup> Rag<sup>-/-</sup> animals are considered superior to SCID mice due to a complete lack of capacity for producing B or T cells and a substantially higher rate of engraftment that reduced variability in the humanization.<sup>294</sup> ILg<sup>c</sup>-/- mice have a severely crippled innate immune response that impacts proper development of acquired immune responses. Crosses with SCID, NOD, and between the lines have produced animals that lack innate and acquired immunity providing an ideal host strain for human immune system engraftment. Using such animals as newborns or adults, another refinement has been made with the advent of CD34+ hematopoietic stem cells (HSC). The HSC act as immune system progenitor cells and, when injected intravenously, intrahepatically or intraperitoneally, can create functional immune organs and cell lineages.<sup>317–321</sup> Following intrahepatic injections, the HSC develop functional human B, T, and dendritic cells including human cells that populate the mouse thymus where they are educated to be tolerant of mouse MHC.<sup>321</sup> These humanized mice have been infected with HIV-1 where persistent viremia,

reduced CD4 cell numbers in blood and thymus and a robust anti-HIV antibody response were observed.<sup>322–325</sup> Importantly, these animals could be infected with HIV-1 via genital or rectal routes common to HIV-1 infection in humans.<sup>324</sup> Although a tremendous step forward modeling HIV-1 infections in a small animal, there are still several concerns with the models regarding robust immunoglobulin responses important to vaccine evaluations and HIV-1 infection of the nervous system and the recently recognized gut-associated lymphoid tissues (GALT) that play an important role in human infection.<sup>326,327</sup>

To address some of these additional concerns, a final refinement has been reported that is a labor-intensive approach to more fully reconstituting a human immune system in these severely immunodeficient mice. The NOD/SCID BLT mouse is considered to be the most advanced model system to date and involves the engraftment of human fetal liver and thymus in the kidney followed by transplantation of autologous CD34+ HSC providing long-term reconstitution of functional lymphoid and myeloid cell lineages.<sup>328–330</sup> BLT mice can produce human immunoglobulin appropriate to challenges or immunization<sup>329,331,332</sup> and support HIV-1 infections via several routes.<sup>333,334</sup> Infected animals produce human antibody against HIV<sup>334</sup> and have been used for antiviral testing following vaginal inoculation.<sup>333</sup> Importantly, the BLT mice have been reported to have a properly colonized GALT, lung, and female reproductive tract making them an attractive alternative for HIV-1 research.<sup>329,333,334</sup>

## HOST RESPONSE

As noted several times, the limited host range of HIV-1 has made modeling of host responses one of the most difficult aspects of this work. Further, the lymphotropic nature of the HIV-1 infection that allows the virus to subvert the immune system by infecting the cells responsible for many aspects of the host response contributes to the difficulties. Non-human primates infected with SIV and SHIV have provided indications of the role of T cells in the response and have indicated novel directions for study in humans. Recently, the trafficking of monocytes and macrophage associated with the development of encephalitis has been compared between non-human primates and clinical conditions.<sup>335</sup> Unfortunately, the SIV macaque models have been able to provide only limited insight into immunoglobulin responses due to the genetic differences in the envelope. The chimeric viruses that are primarily HIV-1 (including *env*) with necessary SIV elements should provide greater insight into the types of antibody that are effective at resolving HIV as well as identifying the epitopes that should be targeted by future vaccines. Perhaps the greatest likelihood of success in this regard will come from the humanized mouse systems that will allow the modeling of specific human responses to HIV-1.

In the SIV/macaque model, infected animals show relatively quick and robust antibody responses as well as non-specific increases in CD8 numbers and NK cell activity in the blood.<sup>336</sup> Cytotoxic lymphocytes are detected in infected animal mucosa

within 3 weeks of inoculation but appear to develop too late or are too limited to effectively resolve the infections.<sup>225,337</sup> Interestingly, it was reported that vaginal infection led to a different emergence of virus-specific T cells that was suggested to be an indication of altered homing.<sup>338</sup> As seen clinically, the immune responses in macaques infected with SIV or SHIV decline over time as the CD4 cell counts diminish.<sup>225</sup> As noted above, the onset of AIDS in infected monkeys is sooner than in human patients further complicating study of the host responses.

As a model of HIV-1 neurological sequelae, FIV infection of domestic cats provides some likely indications of human host responses. All FIV isolates cause neuropathologies that include immune cell infiltrates and gliosis in the midbrain and thalamus.<sup>288,339</sup> Immune responses are activated during the infection and can exacerbate the neuropathology observed and can lead to B cell, CD4, and CD8 cell infiltration of the nervous system.<sup>286</sup> Study of these responses has helped address some of the issues with human neuroAIDS. Finally, the success with a vaccine for FIV has suggested this system may be of great value for directing vaccine work but immune reagents for such studies are lacking. Again, the humanized mouse or the transgenic rabbit, rat or mouse may provide the necessary advancement and available reagents to address the shortcomings in the non-human primate models.

## SUMMARY

By its very nature, HIV-1 presents some of the most difficult aspects for animal modeling of all the STIs. The limited host range of the family of lentiviruses and HIV-1's cell tropism also add to the modeling issues. Despite these shortcomings, researchers have made substantial progress in understanding the virus, the role of key genetic functions, establishing systems for evaluation of antivirals and vaccines using the few available animal systems. It is of note that the creativity of the researchers modeling HIV-1 in animals has led to some major advances for STI research including the advent of chimeric viruses and the humanized mouse. It is even more remarkable given the very recent emergence of this STI.

## Trichomoniasis

While genital infections with *Trichomonas vaginalis* are highly prevalent, there has been a paucity of research using animal models, largely for similar reasons to other animal models for sexually transmitted infections in which the etiologic agents have a high specificity for the human host. An abscess model in the mouse can be induced by intraperitoneal or sub-cutaneous injection<sup>340</sup>; nevertheless, this model does not bear relevance to vaginal infection. Analogous to other models discussed in this chapter, the key factor to establishing trichomonas infection in animals was the manipulation of the hormonal balance. However, since this infection is primarily one of the vaginal infection, it was important to consider the nature of the normal flora and the vaginal pH in the animal model in order to establish infection.

## DESCRIPTION OF THE MODEL AND RELATIONSHIP TO HUMAN DISEASE

### Non-Human Primate

Successful infection of non-human primates was first accomplished by Gardner and colleagues when they inoculated squirrel monkeys (*Saimiri sciureus*) with a single inoculum of  $5 \times 10^5$  *T. vaginalis* cells.<sup>341</sup> Because squirrel monkeys have a trichomonas species as normal flora in the gut, the animals were treated with metronidazole prior to inoculation with *T. vaginalis*. Infection of the animals was only accomplished when they were inoculated during breeding season because they had elevated levels of estradiol, with two of the animals remaining positive for 4 weeks until becoming negative as estrus waned. Microscopic examination of tissues demonstrated an acute and chronic inflammatory response primarily at the squamocolumnar junction of the vagina and cervix.

The only other attempt to develop a non-human primate model was published by Patton and colleagues.<sup>342</sup> In this study, they inoculated pigtailed macaques (*Macaca nemestrina*) with  $6.6 \times 10^5$  trichomonads intravaginally. A high rate of infection was demonstrated with organisms persisting in the majority of the monkeys for up to 5 weeks after which the experiment was terminated. The vaginal pH varied from 5.5 to 8.0 but appeared to be dependent upon the stage of the estrous cycle. In addition, there was no obvious effect of the infection on the normal flora of the animals. In 3 of 8 animals examined by colposcopy, tissue irritation was observed but no "strawberry" cervix as observed in humans. Thus, this model is able to demonstrate consistent infection and has the potential for use in the study of the pathogenesis of infection as well as in the evaluation of topical microbicides and other therapeutic measures.

### Mouse Model

The mouse has been a more difficult animal in which to establish a genital tract infection with *T. vaginalis*. The key to producing a successful infection was the pretreatment of mice with estradiol but the infection could be further enhanced by modifying the normal flora of the mouse.<sup>343,344</sup> Therefore, BALB/c mice were injected subcutaneously with 10 mg/mL of estradiol valerate 2 and 9 days prior to inoculation with *T. vaginalis*. In addition, mice were inoculated with  $10^9$  CFU of *Lactobacillus acidophilus* intravaginally 7 days prior to inoculation with trichomonads. When compared to mice not populated with lactobacilli, there was no difference in the number of mice becoming infected; however, a significantly higher percentage of animals remained infected for at least 24 days after inoculation.<sup>343</sup> Infection in the control mice declined by day 12 and majority of the animals resolved their infections by day 21.

### HOST RESPONSE

Thus, so far there has been only minimal work done on the host response to vaginal infection with *T. vaginalis*. Humans do not

appear to develop immunity to reinfection, and it appears that the mouse mimics this as well. Abraham and colleagues infected mice intravaginally and then treated the mice with metronidazole at 14 days to resolve the infection with the intent of inducing a protective response.<sup>345</sup> However, upon challenge there was no difference in the infection rate or course of infection in the treated mice versus naïve mice, suggesting that immunity did not develop as a result of infection. Interestingly, sub-cutaneous immunization of mice with varying doses of viable trichomonads did result in a protective response and did appear to be correlated with IgG antibodies in sera and secretions. Thus, it was possible to elicit a protective response but genital tract infection alone does not appear to be sufficient.

## SUMMARY

As is apparent from the dearth of literature on animal models of vaginal infection with *T. vaginalis*, there remains a great deal to be done. Nevertheless, the non-human primate and mouse models are potentially useful in the study of the pathogenesis of infection and investigation into possible mechanisms by which the organism apparently avoids a protective host response.

## Co-infection Models

An area that has received little attention but which is very important in the modeling of sexually transmitted infections is the infection of animals with more than one STI agent, obviously, an event that commonly occurs in humans. The following represent initial studies on models of co-infection which will allow for the quantification of the impact of a pre-existing sexually transmitted infection on susceptibility to a second STI. Results of such modeling should help direct subsequent clinical research and may lead to novel approaches of protection against infection as well as the potential influence on disease elicited by each agent.

## CHLAMYDIA SPP./HSV-2

The development of mouse models for vaginal HSV-2 and *Chlamydia spp.* infections that both utilize progesterone preconditioning offers the opportunity for the study of pre-existing infection of one on the other. There have been a number of associations made suggesting genital herpes enhances susceptibility to other pathogens including HIV as a result of the HSV-2-induced vaginal ulceration but few studies have examined the impact on pre-existing STI infection on HSV-2. To study the impact of chlamydial infection on HSV-2 challenge, mice were inoculated with approximately  $1 \times 10^6$  IFU of *C. trachomatis* human serovar E or *C. muridarum* after standard progesterone conditioning. In parallel, a group of similarly conditioned animals was mock inoculated with equal volumes of PBS. Animals were swabbed on day 3 post-infection and assessed by PCR<sup>346</sup> for active chlamydial infection. Three days later (day 6 post-infection) each animal was challenged with HSV-2 and followed for vaginal

viral titer and disease signs. The results indicated a substantial reduction in HSV-2 vaginal titer and disease signs in those mice that had evidence of chlamydial infection regardless of the species (N Bourne and RB Pyles, unpublished data).

## NEISSERIA GONORRHOEAE/CHLAMYDIA

The development of a mouse model to study gonorrhea and chlamydia co-infection is challenged by the fact that female mice are susceptible to *N. gonorrhoeae* and *C. muridarum* at different stages in the reproductive cycle. Recently, a mouse model was described in which mice are first colonized with *C. muridarum* and then challenged with *N. gonorrhoeae*. Interestingly, the number of gonococci recovered is reproducibly higher in *C. muridarum*-infected mice compared to mice inoculated with *N. gonorrhoeae* alone. The vaginal neutrophil response is also higher in co-infected mice than in mice infected with either single pathogen. These results suggest a pre-existing chlamydia infection may promote increased survival or replication of *N. gonorrhoeae* and thus increased susceptibility to gonorrhea (RA Vonck, T Darville, CM O'Connell, and AE Jerse, personal communication). This model should be a valuable system for studying interactions between *Chlamydia* and *N. gonorrhoeae* *in vivo* and the host response to co-infection with these two common pathogens.

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### Summary

The use of animal models for the study of sexually transmitted infections has been critical to our understanding of the pathogenesis of disease and host response to infections as well as the development of intervention and prevention modalities. Nevertheless, none of the animal models are exact substitutes for the human disease, so that in some cases it has been difficult to extrapolate data obtained in the animal directly to the human situation. Thus, the use of specific animal models requires that one understand how the models differ from human disease as much as how they are similar, e.g., whether a different microbial species is used, whether there are significant differences in the physiology of the host compared to humans, or whether the kinetics of the infection are different. For some infectious agents, more than one model is available, with each mimicking a part but not all of the disease as it presents in humans. In such situations, it is important that the investigator understands which model will best answer the particular question being asked and be aware that not every model can answer every question. Choosing the wrong model for a given problem will very likely provide misleading information. The purpose of this chapter is not only to describe the animals models used for the various STIs, but also to present the advantages and disadvantages of the various models and how the models can be applied to understand human disease. This information should aid the investigator in not only interpreting animal model data in the context of human disease but also provide the researcher with the information necessary to choose an animal model for their work.



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# section **xvi**

## **GUIDELINES FOR THE MANAGEMENT OF SEXUALLY TRANSMITTED DISEASES AND HIV**

— *Basil Donovan*

Guidelines for the Management of Sexually Transmitted Infections	1299
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## Introduction

Effective management of sexually transmitted infections (STIs) is an important component of STI control, as it reduces the further transmission of infections, prevents the development of complications, and serious long-term sequelae. Rapid and effective treatment of STIs also leads to the reduction in the transmission of the human immunodeficiency virus (HIV).<sup>1,2</sup>

Provision of appropriate treatment of STIs at the first contact a patient has with a healthcare provider is an important public health intervention as it reduces the infectivity of the patient and allows for the provision of behavior change communication, while there is the potential to influence future sexual behavior and treatment-seeking practices. The World Health Organization strongly recommends that all countries develop and use standardized treatment protocols for STIs.<sup>3</sup> Having such guidelines ensure that all patients receive adequate high-quality care at all levels of the health service. In addition, standardized guidelines facilitate the training of care providers and the procurement and distribution of antimicrobial agents. The use of standardized treatment recommendations at the national level helps to reduce the risk of development of resistance to antimicrobials.

Recommendations described in this chapter will help countries to develop standardized protocols that are adapted to address local epidemiological and antimicrobial sensitivity patterns. It cannot be over-emphasized that it is essential that antimicrobial susceptibility of STI pathogens are monitored closely as pathogens resistant to recommended antimicrobials may emerge spontaneously or may be imported from other parts of the world.

## STI Case Management

STI case management is the provision of the complete care “package” to a person with an STI that may have been diagnosed syndromically or after laboratory tests have been performed. The components of case management include:

- history taking;
- clinical examination;

- making a diagnosis, which may be syndromic or etiologic;
- provision of effective treatment;
- provision of behavior change communication, including: information on the nature of infection, acquisition and transmission of infection, prevention of infection, and advice on safer sexual behavior;
- promotion and provision of condoms, together with education on the correct use of condoms and their hygienic disposal;
- partner notification and treatment;
- case reporting; and
- clinical follow-up as appropriate.

Thus, effective case management consists not only of antimicrobial therapy to obtain cure and reduce infectivity, but also comprehensive consideration and care of the patient’s reproductive health.

## Syndromic Management of STIs

The diagnosis of STIs may be made upon the laboratory identification of a sexually transmissible pathogen or on the recognition of the pattern of symptoms and signs an infected person presents with.

Making an etiologic diagnosis based upon identifying the pathogen requires laboratory testing, and this is problematic for healthcare providers in many settings, especially in the primary healthcare setting where the infected person first presents for care. Laboratory testing places constraints on time and resources, increases costs and reduces access to treatment. It is also dependent on the availability of appropriate laboratory tests. Currently only a few tests that have high sensitivities and specificities that can be performed at the point of care are available commercially. Hence the making of an etiologic diagnosis requires that specimens be collected and sent to central level laboratories for processing. This results in unacceptable delays in providing the patient with care. Laboratories require suitably qualified personnel with adequate training to perform technically demanding procedures, and the establishment of external quality control must be made mandatory.



The syndromic management approach is based on the identification of consistent groups of symptoms and easily recognized signs (syndromes), and the provision of treatment that will deal with the majority of, or the most serious, organisms responsible for producing a syndrome. WHO has developed a simplified tool (a flowchart or algorithm) to guide health workers in the implementation of syndromic management of STIs.

Many healthcare facilities in developing countries lack the equipment and trained personnel required for etiological diagnosis of STIs. To overcome this problem, a syndrome-based approach to the management of STI patients has been developed and promoted in a large number of countries in the developing world.

Readers are advised to read Section 9 on the syndromic management of sexually transmitted infections, which describes the approach in greater detail.

### SELECTION OF ANTIMICROBIAL REGIMENS

When selecting antimicrobial regimens for specific STIs, a number of important points need to be considered. These include drug efficacy, drug safety, the cost of the drugs, and acceptability of the recommended regimen to the patient in order to ensure treatment compliance, local availability of the drugs, and the effect of the drug regimen on co-infections.

#### Drug Efficacy

An important criterion when selecting an antimicrobial is the effectiveness of the drug in treating the infection. Ideally the recommended drug regimen should cure at least 95% of those with the infection. Drug regimens with lower cure rates of between 85% and 95% should be used only with caution as such treatments may select for resistant strains and therefore rapidly limit their usefulness. Regimens with lower cure rates should not be recommended.<sup>3</sup>

Often efficacy data cannot be transferred reliably from one population (or in some situations, from one sub-population) to another. Therefore, ideally, recommendations should be based on well-designed therapeutic trials conducted locally. Of course, this will depend on the local availability of expertise and financial resources to conduct such trials. In such situations, recommendations may be based on evidence obtained from studies conducted within the region.

Therapeutic efficacy of antimicrobials should be monitored; this requires periodic studies of clinical efficacy and laboratory monitoring for antimicrobial susceptibility of STI pathogens.<sup>4</sup>

#### Drug Safety

The safety of recommended drugs is an important consideration when developing treatment guidelines. The occurrence of adverse drug reactions is not in general predictable and reactions range from minor discomfort to major life-threatening events. However, there is always a need to keep this in mind when making recommendations. Intolerance to drugs often leads to non-compliance with treatment regimens and hence infected patients may only be partially treated and risk further transmission of

infection as symptoms may be masked. It should also be noted that combination drug regimens further increase the risk of adverse drug reactions and intolerance. In addition, it is necessary that certain drugs are to be avoided during pregnancy and lactation, and considerations of fetal safety are also important when treating pregnant women. It is always, therefore, necessary to have alternate drug regimens that can be used by persons that are unable to take certain medications and for pregnant and lactating women.

#### Cost of Drugs

The cost of drugs is a major limiting factor in all locations. It is assumed that local programs will use the best regimens that they can afford. In calculating the total cost of various regimens, however, it is important to consider the costs associated with less effective therapies: repeat treatment, further transmission of infection, complications, and selection for increased microbial resistance.

More effective but expensive drugs should not be reserved for referral centres. The use of less effective regimens at the primary care level quickly discourages patients from seeking the most readily and rapidly available care and fosters the transmission of infection and the risk of antimicrobial resistance developing to selected antibiotics.

#### Treatment Compliance and Acceptability of Treatment Regimen

Patient compliance with STI treatment regimens is a problem which seriously limits the effectiveness of multi-dose regimens such as those involving erythromycin and tetracyclines. Single-dose or very-short-course regimens are therefore preferred. Appropriate counselling and education have been shown to increase compliance and should be a part of clinical management.

In some societies, oral regimens are strongly preferred to injections, whereas among other groups injection may be seen as the only acceptable form of treatment. In view of the emergence and spread of HIV infection, preference should be given to oral regimens in order to reduce the risks associated with the reuse of non-sterilized injection equipment. Patient education on the efficacy of oral preparations must be included in STI management.

#### Drug Availability

The geographical distribution and availability of drugs vary considerably. The regional availability of some excellent drugs could be improved by their inclusion in the national essential drugs lists.

#### Co-existent Infections

When several STIs are prevalent in a population, co-infection may be a common occurrence. Unfortunately, the ability to treat common co-infections with single drugs has not been established widely. *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are common causes of urethritis and cervicitis. It has become standard practice to treat patients with these conditions for both infections

simultaneously. Until further studies are conducted to show the efficacy of a single antimicrobial agent in treating both infections we remain with having to give two different treatment regimens for these two infections.

## TREATMENT RECOMMENDATIONS FOR SPECIFIC SEXUALLY TRANSMITTED INFECTIONS

The following paragraphs provide a summary of the current treatment recommendations for specific STIs. The recommendations have been extracted from guidelines developed by the World Health Organization, Geneva,<sup>3</sup> the Centers for Disease Control, Atlanta, US<sup>5</sup> and the European Union.<sup>6</sup> Recommendations between the different sources vary slightly but provide readers with a broader selection of antimicrobials to choose from, when developing their own National guidelines.

### Gonorrhea

#### Uncomplicated Gonorrhea

Uncomplicated gonorrhea includes gonococcal urethritis, cervicitis, pharyngitis, and proctitis in adults. Table 113.1 summarizes the recommendations for the treatment of uncomplicated gonococcal infection in men and women. Gonococcal pharyngeal infection is difficult to eradicate completely and none of the antibiotics has an efficacy of greater than 90%. The recommended treatment for gonococcal pharyngeal infection is intramuscular ceftriaxone.

**Table 113.1:** Recommendations for the Treatment of Uncomplicated Gonococcal Infection in Adult Males and Females

#### World Health Organization:

Ceftriaxone, 250 mg by intramuscular injection (IM).  
Alternatively, the following may be used:  
Cefixime, 400 mg orally (PO), Or  
Spectinomycin 2 g IM, Or  
Ciprofloxacin, 500 mg PO—to be used only in those areas where there is documented evidence of ongoing sensitivity of *N. gonorrhoeae* to quinolones.

#### Centers for Disease Control:

Ceftriaxone, 125 mg IM, Or  
Cefixime, 400 mg PO.  
Alternatively, the following may be used:  
Cefpodoxime, 400 mg PO, Or  
Cefuroxime axetil, 1 g PO, Or  
Ceftizoxime, 500 mg IM, Or  
Azithromycin, 2 g PO, Or  
Cefoxitin, 2 g IM plus probenecid 1 g PO  
Cefotaxime, 500 mg IM, Or  
Spectinomycin, 2 g IM.

#### European Guidelines

Ceftriaxone, 250 mg IM.  
Alternatively, the following may be used:  
Cefixime, 400 mg PO, Or  
Spectinomycin, 2 g IM.

Note: In pregnant and lactating women, doxycycline, tetracycline, and fluoroquinolones should not be used.

### Gonococcal Conjunctivitis in Adults

This is a serious condition that requires systemic therapy. Infection of the conjunctiva occurs as a result of auto-inoculation of genital secretions. Education on hand washing and personal hygiene is an important component in the management of patients with this condition. Table 113.2 summarizes the treatment recommendations.

#### Neonatal Gonococcal Conjunctivitis

Neonates may become infected with *N. gonorrhoeae* at the time of birth if the mother has the infection. Gonococcal neonatal conjunctivitis, also known as gonococcal ophthalmia neonatorum, is a serious infection as it may lead to perforation of the globe and results in blindness. It is a preventable infection and ophthalmia prophylaxis should be performed routinely for all babies born to mothers living in areas where gonorrhea prevalence is significant. It may also be prevented if maternal infection is diagnosed and adequately treated before the birth of the baby. Table 113.3 summarizes the recommended treatment of neonatal gonococcal conjunctivitis.

#### Prevention of Ophthalmia Neonatorum

Gonococcal ophthalmia neonatorum is preventable with timely eye prophylaxis. WHO advises that the infant's eyes should

**Table 113.2:** Recommendations for the Treatment of Gonococcal Conjunctivitis in Adult Males and Females

#### World Health Organization:

Ceftriaxone, 250 mg IM.  
Alternatively, the following may be used:  
Spectinomycin, 2 g IM, Or  
Kanamycin, 2 g IM.

Note: Though published data are not available it is felt by experts that this treatment regimen is efficacious in treating this condition.

#### Centers for Disease Control:

Ceftriaxone, 1 g IM.  
Note: This recommendation is based on the results of one small study and on expert opinion.

Note: Local administration of antibiotic eye ointment is not recommended but irrigation the eyes with normal saline may be useful.

**Table 113.3:** Recommendations for the Treatment of Neonatal Gonococcal Conjunctivitis

#### World Health Organization:

Ceftriaxone, 50 mg/kg IM single dose (maximum dose 125 mg).  
Alternatively, the following may be used:  
Kanamycin, 25 mg/kg IM single dose (maximum dose 75 mg), Or  
Spectinomycin, 25 mg/kg IM single dose (maximum dose 75 mg).

#### Centers for Disease Control:

Ceftriaxone 25–50 mg/kg IM single dose (maximum dose 125 mg).

#### European Guidelines

Ceftriaxone 25–50 mg/kg IM single dose (maximum dose 125 mg), Or  
Cefotaxime 100 mg/kg IM single dose.

Note: Irrigation of eyes with normal saline is recommended.

be carefully cleaned immediately after birth. The application of 1% silver nitrate solution or 1% tetracycline ointment to the eyes of all infants at the time of delivery is strongly recommended as a prophylactic measure. However, ocular prophylaxis provides poor protection against *C. trachomatis* conjunctivitis. Infants born to mothers with gonococcal infection should receive: ceftriaxone, 50 mg/kg IM single dose, to a maximum of 125 mg.

Alternatively, where ceftriaxone is not available: kanamycin, 25 mg/kg IM single dose to a maximum of 75 mg or spectinomycin 25 mg/kg IM single dose to a maximum of 75 mg may be used.

### Disseminated Gonococcal Infection

Disseminated gonococcal infection results from gonococcal bacteremia. The condition causes a sparse distal pustular or petechial rash, and an asymmetric arthralgia, tenosynovitis or septic arthritis. The infection may be complicated by perihepatitis and rarely by endocarditis or meningitis. Some strains of *N. gonorrhoeae* that cause disseminated infection may produce minimal genital inflammation. Table 113.4 summarizes the treatment recommendations.

**Table 113.4:** Recommendations for the Treatment of Disseminated Gonococcal Infection

#### World Health Organization:

Ceftriaxone, 1 g IM or intravenously (IV) daily for 7 days

Alternatively, the following may be used:

Spectinomycin, 2 g IM twice daily for 7 days

*Note:* For gonococcal meningitis, treatment is continued for 14 days and for endocarditis the duration of therapy will need to be increased to 4 weeks

#### Centers for Disease Control:

Ceftriaxone, 1 g IM or intravenously (IV) daily for 7 days

Alternatively, the following may be used:

Cefotaxime, 1 g IV every 8 hours, Or

Ceftizoxime, 1 g IV every 8 hours, Or

Spectinomycin, 2 g IM twice daily

This treatment is continued for 24–48 hours after improvement begins and then the patient may be treated with cefixime, 400 mg PO daily; the total duration of antibiotics should not be less than 7 days

*Note:* For gonococcal meningitis IM or IV treatment is continued for 14 days and for endocarditis the duration of IM or IV therapy should be 4 weeks

#### European guidelines

Ceftriaxone, 1 g IM or intravenously (IV) daily for 7 days

Alternatively, the following may be used:

Cefotaxime, 1 g IV every 8 hours, Or

Spectinomycin, 2 g IM twice daily

This treatment is continued for 24–48 hours after improvement begins and then the patient may be treated with cefixime, 400 mg PO daily Or if quinolone resistance is excluded ciprofloxacin, 500 mg PO twice daily; the total duration of antibiotics should not be less than 7 days.

*Note:* For gonococcal meningitis IM or IV treatment is continued for 14 days and for endocarditis the duration of IM or IV therapy should be 4 weeks

*Note:* In pregnant and lactating women, doxycycline, tetracycline, and fluoroquinolones should not be used.

## C. trachomatis Infections other than Lymphogranuloma Venereum

### Anogenital Chlamydial Infection

Anogenital chlamydial infection includes infection of the urethra, cervix, and rectum with *C. trachomatis*. Recommended regimens are shown in Table 113.5.

### Chlamydial Infection during Pregnancy

Recommendations for the treatment of chlamydial infections during pregnancy are shown in Table 113.6.

### Neonatal Chlamydial Conjunctivitis

The following are recommendations (Table 113.7) for the treatment of neonatal chlamydial conjunctivitis. It is however

**Table 113.5:** Recommendations for the Treatment of Anogenital Chlamydial Infection

#### World Health Organization:

Azithromycin, 1 g PO single dose, Or

Doxycycline, 100 mg PO 12 hourly for 7 days

Alternatively, the following may be used:

Amoxycillin, 500 mg PO 8 hourly for 7 days, Or

Erythromycin, 500 mg PO 6 hourly for 7 days, Or

Ofloxacin, 300 mg PO 12 hourly for 7 days, Or

Tetracycline, 500 mg PO 6 hourly for 7 days

#### Centers for Disease Control:

Azithromycin, 1 g PO once, Or

Doxycycline, 100 mg PO 12 hourly for 7 days

Alternatively, the following may be used:

Erythromycin base, 500 mg PO 6 hourly for 7 days, Or

Erythromycin ethylsuccinate, 800 mg PO 6 hourly for 7 days, Or

Ofloxacin, 300 mg PO 12 hourly for 7 days, Or

Levofloxacin, 500 mg PO once daily for 7 days

#### European guidelines

Azithromycin, 1 g PO once, Or

Doxycycline, 100 mg PO 12 hourly for 7 days

Alternatively, the following may be used:

Erythromycin base, 500 mg PO 6 hourly for 7 days, Or

Ofloxacin, 300 mg PO 12 hourly for 7 days

*Note:* In pregnant and lactating women, doxycycline, tetracycline, and fluoroquinolones should not be used.

**Table 113.6:** Recommendations for the Treatment of Chlamydial Infection during Pregnancy

#### World Health Organization:

Erythromycin, 500 mg PO 6 hourly for 7 days, Or

Azithromycin 1 g PO single dose

Alternatively, the following may be used:

Amoxycillin, 500 mg PO 8 hourly for 7 days, Or

*Note:* In pregnant and lactating women doxycycline, tetracycline, and ofloxacin should not be used

#### Centers for Disease Control:

Azithromycin, 1 g PO once, Or

Amoxycillin, 500 mg PO 8 hourly for 7 days

Alternatively, the following may be used:

Erythromycin base, 500 mg PO 6 hourly for 7 days, Or

Erythromycin base, 250 mg PO 6 hourly for 14 days, Or

Erythromycin ethylsuccinate, 800 mg PO 6 hourly for 7 days



**Table 113.7:** Recommendations for the Treatment of Neonatal Chlamydial Conjunctivitis**World Health Organization:**

Erythromycin syrup, 50 mg/kg/day PO, in four divided doses for 14 days

Alternatively, the following may be used:

Trimethoprim, 40 mg with sulfamethoxazole, 200 mg PO, twice daily for 14 days

**Centers for Disease Control:**

Erythromycin syrup, 50 mg/kg/day PO, in four divided doses for 14 days

advisable to treat all newborn infants with conjunctivitis for both *N. gonorrhoeae* and *C. trachomatis*, because of the possibility of mixed infection.

**Infantile Chlamydial Pneumonia**

Recommendations for the treatment of chlamydial pneumonia in infants are summarized in Table 113.8.

**Syphilis**

Syphilis is a systemic infection and if untreated may lead to serious long-term complications. Syphilis may be transmitted transplacentally from an infected pregnant woman to her fetus and it may be transmitted from person to person through sexual intercourse. The infection is divided into congenital and acquired categories and within both categories there may be early and late stages. Early syphilis is defined as infection of less than 2 years duration and includes the primary, secondary, and latent stages. Late syphilis is defined as syphilis of more than 2 years duration and refers to late latent syphilis, gummatous, neurological, and cardiovascular syphilis. **Centers for Disease Control (CDC)** defines early syphilis as syphilis of less than 1 year duration and late syphilis as syphilis of more than 1 year's duration.

**Early Acquired Syphilis (Primary, Secondary, and Early Latent Syphilis)**

Table 113.9 summarizes the treatment recommendations for early acquired syphilis.

**Late Latent Acquired Syphilis (Latent Infection of >2 Year's duration or of Unknown Duration)**

Table 113.10 summarizes the recommendations for the treatment of late latent syphilis.

**Table 113.8:** Recommendations for the Treatment of Neonatal Chlamydial Pneumonia**World Health Organization:**

Erythromycin syrup, 50 mg/kg/day PO, in four divided doses for 14 days

**Centers for Disease Control:**

Erythromycin syrup, 50 mg/kg/day PO, in four divided doses for 14 days

**Table 113.9:** Recommendations for the Treatment of Early Acquired Syphilis**World Health Organization:**

Benzathine benzylpenicillin, 2.4 million IU IM, at a single session (because of the volume involved, this dose is usually given as two injections at separate sites)

Alternatively the following may be used.

Azithromycin, 2 g PO single dose, Or

Procaine benzylpenicillin, 1.2 million IU IM daily for 10 consecutive days, Or

Doxycycline, 100 mg PO 12 hourly for 14 days, Or

Tetracycline, 500 mg PO 6 hourly for 14 days

*Note:* In penicillin-allergic patients Azithromycin 2 g PO single dose is given. Alternatively erythromycin, 500 mg PO 6 hourly is given for 14 days

**Centers for Disease Control:**

Benzathine benzylpenicillin, 2.4 million IU IM, at a single session

*Note:* In penicillin-allergic patients, de-sensitization should be considered and benzathine benzylpenicillin is then given

Doxycycline, 100 mg PO 12 hourly for 14 days or tetracycline. 500

mg PO 6 hourly for 14 days may be considered

**European guidelines**

Benzathine penicillin 2.4 million units IM (1.2 million units IM into each buttock)

Alternatively, the following may be given:

Azithromycin, 2 g PO single dose, Or

Procaine benzylpenicillin, 600,000 IU IM daily for 10–14 days, Or

Doxycycline, 100 mg PO 12 hourly for 14 days, Or

Tetracycline, 500 mg PO 6 hourly for 14 days, Or

Erythromycin, 500 mg PO 6 hourly for 14 days

*Note:* In penicillin-allergic patients, Azithromycin 2 g PO single dose is given. Alternatively erythromycin, 500 mg PO 6 hourly is given for 14 days

*Note:* In pregnant and lactating women, doxycycline, tetracycline, and fluoroquinolones should not be used.

**Table 113.10:** Recommendations for the Treatment of Late Latent Acquired Syphilis**World Health Organization:**

Benzathine benzylpenicillin, 2.4 million IU IM once weekly for 3 weeks

Alternatively, the following may be used:

Procaine benzylpenicillin, 1.2 million IU IM daily for 20 consecutive days, Or

*Note:* In penicillin-allergic patients use Doxycycline, 100 mg PO 12 hourly for 30 days, Or

Tetracycline, 500 mg PO 6 hourly for 30 days and in pregnant women

allergic to penicillin use erythromycin, 500 mg PO 6 hourly is given for 30 days

**Centers for Disease Control:**

Benzathine benzylpenicillin, 2.4 million IU IM once weekly for 3 weeks

*Note:* In penicillin-allergic patients, Doxycycline, 100 mg PO 12 hourly for 14 days or tetracycline 500 mg PO 6 hourly for 14 days may be given

In penicillin-allergic pregnant women, desensitization should be carried out and then the patient is treated with benzathine penicillin

**European guidelines**

Benzathine penicillin 2.4 million units IM (1.2 million units IM into each buttock)

Alternatively, the following may be given

Procaine benzylpenicillin, 600,000 IU IM daily for 17–21 days, Or

*Note:* In penicillin-allergic patients, Doxycycline, 100 mg PO 12 hourly for 21–28 days, Or

Tetracycline, 500 mg PO 6 hourly for 28 days

If the patient is a penicillin-allergic pregnant woman then give

Erythromycin, 500 mg PO 6 hourly for 28 days

*Note:* In pregnant and lactating women, doxycycline, tetracycline, and fluoroquinolones should not be used.

**Late Acquired Syphilis (Gummatous and Cardiovascular Syphilis)**

The CDC guidelines for the management of gummatous syphilis and cardiovascular syphilis are shown in Table 113.11A.

**Late Acquired Neurosyphilis**

Recommendations for the management of neurosyphilis are shown in Table 113.11B. Neurologic involvement by syphilis may occur in any stage of syphilis. Once a diagnosis is made then the patient is treated for neurosyphilis as shown in Table 113.11B.

**Table 113.11A:** Recommendations for the Treatment of Late Acquired Syphilis (Gummatous and Cardiovascular Syphilis)

**Centers for Disease Control:**

Benzathine benzylpenicillin, 2.4 million IU IM once weekly for 3 weeks

*Note:* In penicillin-allergic patients Doxycycline, 100 mg PO 12 hourly for 28 days or tetracycline, 500 mg PO 6 hourly for 28 days may be given. In penicillin-allergic pregnant women desensitization should be carried out and then the patient is treated with benzathine penicillin

**Table 113.11B:** Recommendations for the Treatment of Acquired Neurosyphilis

**World Health Organization:**

Aqueous benzylpenicillin, 12–24 million IU/day by intravenous injection and administered in doses of 2–4 million IU, every 4 hours for 14 days

Alternatively, the following may be used:

Procaine benzylpenicillin, 1.2 million IU IM once daily together with Probenecid 500 mg PO four times daily, both for 10–14 days (This regimen should be used only for patients whose outpatient compliance can be assured)

*Note:* In penicillin-allergic non-pregnant patients, Doxycycline, 200 mg orally, twice daily for 30 days Or Tetracycline, 500 mg orally, four times daily for 30 days may be used.

**Centers for Disease Control:**

Aqueous benzylpenicillin, 12–24 million IU/day by intravenous injection and administered in doses of 2–4 million IU, every 4 hours for 14 days

Alternatively, the following may be used if compliance can be assured:

Procaine benzylpenicillin, 1.2 million IU IM once daily together with Probenecid 500 mg PO four times daily, both for 10–14 days

*Note:* Ceftriaxone can be used as an alternative treatment for patients with neurosyphilis, although the possibility of cross-reactivity between this agent and penicillin exists. Some specialists recommend ceftriaxone, 2 g daily either IM or IV for 10–14 days. Other regimens have not been adequately evaluated for treatment of neurosyphilis. Therefore, if concern exists regarding the safety of ceftriaxone for a patient with neurosyphilis, the patient should obtain skin testing to confirm penicillin allergy and, if necessary, be desensitized and managed in consultation with a specialist.

**European guidelines**

Aqueous benzylpenicillin, 12–24 million IU/day by intravenous injection and administered in doses of 2–4 million IU, every 4 hours for 14 days

Alternatively, the following may be used:

Procaine benzylpenicillin, 1.2 million IU IM once daily together with Probenecid, 500 mg PO four times daily, both for 10–14 days (This regimen should be used only for patients whose outpatient compliance can be assured)

*Note:* In penicillin-allergic non-pregnant patients Doxycycline, 200 mg orally, twice daily for 30 days can be used.

**Early Congenital Syphilis (up to 2 Years of Age) and Infants with Abnormal Cerebrospinal Fluid**

Recommendations for the treatment of early congenital syphilis and infants with syphilis who have an abnormal CSF are shown in Table 113.12. Effective prevention and detection of congenital syphilis depends on the identification of syphilis in pregnant women and, therefore, on the routine serologic screening of pregnant women during the first prenatal visit. In communities and populations in which the risk for congenital syphilis is high, serologic testing and a sexual history also should be obtained at 28 weeks' gestation and at delivery. Moreover, as a part of the management of pregnant women who have syphilis, information concerning treatment of sex partners should be obtained to assess the risk for reinfection.

**Congenital Syphilis of >2 Years Duration**

Table 113.13 shows the WHO guidelines on the management of congenital syphilis in children over the age of 2 years.

**Genital Herpes**

The primary cause of genital herpes is infection with the herpes simplex virus Type 2 (HSV2). This STI is highly prevalent throughout the world and has become the commonest cause of genital ulcer disease worldwide. The major public health importance of HSV2 relates to its potential role in facilitating HIV transmission. There is no known cure for genital herpes, but

**Table 113.12:** Recommendations for the Treatment of Early Congenital Syphilis

**World Health Organization:**

Aqueous benzylpenicillin 100,000–150,000 IU/kg/day administered as 50,000 IU/kg/dose IV every 12 hours, during the first 7 days of life and every 8 hours thereafter for a total of 10 days, Or Procaine benzylpenicillin, 50,000 IU/kg by intramuscular injection, as a single daily dose for 10 days

*Note:* Some experts treat all infants with congenital syphilis as if the CSF findings were abnormal. Antimicrobials other than penicillin (e.g., erythromycin) are not indicated for congenital syphilis except in cases of severe allergy to penicillin. Tetracyclines should not be used in young children.

**Centers for Disease Control:**

Aqueous crystalline penicillin G 100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days, Or Procaine penicillin G 50,000 units/kg/dose IM in a single daily dose for 10 days

**Table 113.13:** Recommendations for the Management of Congenital Syphilis in Children over the Age of 2 Years

**World Health Organization:**

Aqueous benzylpenicillin, 200,000–300,000 IU/kg/day by intravenous or intramuscular injection, administered as 50,000 IU/kg every 4–6 hours for 10–14 days

Alternatively, the recommended regimen for penicillin-allergic patients, after the first month of life is erythromycin, 7.5–12.5 mg/kg orally, four times daily for 30 days

the course of symptoms can be modified if systemic therapy with anti-herpes-virus agents. Treatment with aciclovir, or its analogs, needs to be started as soon as possible following the onset of symptoms. Treatment can be expected to reduce the formation of new lesions, the duration of pain, the time required for healing, and viral shedding. Treatment, however, does not influence the natural history of recurrent disease. Treatment recommendations vary depending on the clinical stage of the infection.

### First Clinical Episode of Genital Herpes

Table 113.14 summarizes the recommendations for the treatment of the first clinical episode of genital herpes.

### Treatment of Recurrent Episodes

Treating episodes of recurrences is beneficial in that it reduces the duration of the attack and reduces the amount of viral shedding from lesions. Treatment should be commenced within 24 hours of the onset of the prodromal symptoms. The above treatments are used with the difference being that the treatment course can be shortened to 5 days. Shorter courses of these treatments may also be useful if the dose of the antiviral agent is increased: Aciclovir, 800 mg, orally twice a day for 5 days, Aciclovir, 800 mg, orally three times a day for 2 days, Famciclovir, 1000 mg, orally twice daily for 1 day, and Valacyclovir, 500 mg, orally twice a day for 3 days.

In persons with HIV infection, episodic treatment is advised as follows: Aciclovir, 400 mg, orally three times a day for 5–10 days, or Famciclovir, 500 mg, orally twice a day for 5–10 days, or Valacyclovir, 1.0 g, orally twice a day for 5–10 days.

### Suppressive Treatment

Suppressive therapy reduces the frequency of genital herpes recurrences by 70–80% in patients who have frequent recurrences (i.e., >6 recurrences/year), and many patients report no symptomatic outbreaks. Treatment also is effective in patients with less frequent recurrences. Safety and efficacy have been documented among patients receiving daily therapy with aciclovir for as long as 6 years

**Table 113.14:** Recommendations for the Treatment of the First Clinical Episode of Genital Herpes

#### World Health Organization:

Aciclovir, 200 mg orally, five times daily for 7 days, Or  
Aciclovir, 400 mg orally, three times daily for 7 days, Or  
Famciclovir, 250 mg, three times daily for 7 days, Or  
Valacyclovir, 1 g, twice daily for 7 days

#### Centers for Disease Control:

Aciclovir, 200 mg orally, five times daily for 7–10 days, Or  
Aciclovir, 400 mg orally, three times daily for 7–10 days, Or  
Famciclovir, 250 mg, three times daily for 7–10 days, Or  
Valacyclovir, 1 g, twice daily for 7–10 days

Note: Recent European guidelines on the treatment of genital herpes are not available; however, the British Association for Sexual Health and HIV (BASHH) has the same recommendations with the difference being that BASHH advises treatment for 5 days.

**Table 113.15:** Recommendations for Suppressive Therapy in Persons with Frequent Recurrences

#### World Health Organization and Centers for Disease Control:

Aciclovir, 400 mg orally, twice daily, Or  
Famciclovir, 250 mg orally, twice daily, Or  
Valacyclovir, 500 mg orally, once daily, Or  
Valacyclovir, 1000 mg orally, once daily

and with valacyclovir or famciclovir for 1 year. Quality of life frequently is improved in patients with frequent recurrences who receive suppressive therapy, compared with episodic treatment. Table 113.15 summarizes the treatment recommendations for long-term suppressive therapy for genital herpes.

Suppressive treatment may be given on a long-term basis to persons with genital herpes who are also HIV infected as follows: Aciclovir, 400–800 mg orally, twice to three times a day, or Famciclovir, 500 mg orally, twice a day, or Valacyclovir, 500 mg orally, twice a day.

In persons with severe disease, intravenous aciclovir may be used in the following doses:

Aciclovir, 5–10 mg/kg IV, every 8 hours for 5–7 days or until clinical resolution is attained.

In neonates with neonatal herpes the following is recommended: Aciclovir, 10 mg/kg intravenously, three times a day for 10–21 days.

### Trichomoniasis

Trichomoniasis is caused by the protozoan *Trichomonas vaginalis*. Infection in women usually leads to vaginal discharge that is malodorous, profuse, and green-yellow in color and often with vulvar irritation. Some women with infection may have no symptoms. Men who are infected with *T. vaginalis* may have no symptoms or they may have a urethral discharge.

Vaginal trichomoniasis has been associated with adverse pregnancy outcomes, particularly premature rupture of membranes, preterm delivery, and low birth weight. However, data do not suggest that metronidazole treatment results in a reduction in perinatal morbidity. Although some trials suggest the possibility of increased prematurity or low birth weight after metronidazole treatment.

Table 113.16 summarizes the treatment recommendations for trichomoniasis.

### Bacterial Vaginosis

Bacterial vaginosis is the commonest cause of vaginal discharge and vaginal malodor. The condition causes the appearance of a sticky discharge, which is greyish in color. It is caused by the replacement of the normal hydrogen peroxide producing lactobacilli by high concentrations of *Gardnerella vaginalis*, *Mycoplasma hominis*, and anaerobic bacteria that include *Mobiluncus sp* and *Prevotella sp*. More than 50% of women with bacterial vaginosis are asymptomatic. Bacterial vaginosis is considered to be an endogenous reproductive tract infection and treatment of sexual partners has not been demonstrated to be of benefit. It is however associated with having



**Table 113.16:** Recommendations for the Treatment of Trichomoniasis in Men and Women**World Health Organization:**

Metronidazole, 2 g orally, in a single dose, Or  
Tinidazole, 2 g orally, in a single dose

*Alternative regimen*

Metronidazole, 400 mg or 500 mg orally, twice daily for 7 days, Or  
Tinidazole, 500 mg orally, twice daily for 5 days

*Note:* In men the 7-day regimen of metronidazole or the 5-day regimen of tinidazole is preferred.

**Centers for Disease Control:**

Metronidazole, 2 g orally, in a single dose, Or  
Tinidazole, 2 g orally, in a single dose

*Alternative Regimen*

Metronidazole, 500 mg orally, twice a day for 7 days

**European guidelines**

Metronidazole, 2 g orally, in a single dose, Or  
Metronidazole, 400–500 mg, twice daily for 5–7 days

*Alternative regimen*

Tinidazole, 2 g orally, in a single dose

multiple sex partners, a new sex partner, douching, and lack of vaginal lactobacilli. Treatment of male sex partners has not been beneficial in preventing the recurrences.

During pregnancy, bacterial vaginosis is associated with adverse pregnancy outcomes including premature rupture of the membranes, preterm labor, preterm birth, intra-amniotic infection, and post-partum endometritis. Treatment recommendations are summarized in Table 113.17.

**Candidiasis****Table 113.17:** Recommendations for the Treatment of Bacterial Vaginosis**World Health Organization recommendations:**

Metronidazole, 400 mg or 500 mg orally, twice daily for 7 days

*Alternative regimen*

Metronidazole, 2 g orally, as a single dose, Or  
Clindamycin, 2% vaginal cream, 5 g intravaginally, at bedtime for 7 days, Or

Metronidazole, 0.75% gel, 5 g intravaginally, twice daily for 5 days, Or  
Clindamycin, 300 mg orally, twice daily for 7 days

**Centers for Disease Control recommendations:**

Metronidazole, 500 mg orally, twice a day for 7 days, Or  
Metronidazole gel, 0.75%, one full applicator (5 g) intravaginally, once a day for 5 days, Or  
Clindamycin cream, 2%, one full applicator (5 g) intravaginally at bedtime for 7 days

*Alternative regimens*

Clindamycin, 300 mg orally, twice a day for 7 days, Or  
Clindamycin ovules, 100 mg intravaginally, once at bedtime for 3 days

**European guidelines**

Metronidazole, 400–500 mg twice daily for 5–7 days, Or  
Metronidazole, 2 g, single dose

*Alternative regimens*

Intravaginal metronidazole gel (0.75%) once daily for 5 days, Or  
Intravaginal clindamycin cream (2%) once daily for 7 days, Or  
Clindamycin, 300 mg, twice daily for 7 days, Or  
Tinidazole, 2 g, single dose

Vulvovaginal candidiasis usually is caused by the yeast *Candida albicans* but occasionally it is caused by other *Candida* sp. Symptoms of infection include pruritus, vaginal soreness, dyspareunia, and abnormal vaginal discharge. It is estimated that 75% of women will have at least one episode of vulvovaginal candidiasis, and 40–45% will have two or more episodes. Vulvovaginal candidiasis is usually not acquired through sexual intercourse. Although treatment of sexual partners is not recommended, partner treatment may be considered for women who have recurrent infection. A minority of male partners may have balanitis, which is characterized by erythema of the glans penis or inflammation of the glans penis and foreskin (balanoposthitis).

Treatment recommendations are summarized in Table 113.18.

**Lymphogranuloma Venereum**

Lymphogranuloma venereum (LGV) is caused by *C. trachomatis* serovars L1, L2, or L3. In heterosexual men, infection leads to a transient genital ulcer at the site of infection followed

**Table 113.18:** Recommendations for the Treatment of Vulvovaginal Candidiasis**World Health Organization:**

Miconazole or clotrimazole, 200 mg intravaginally, daily for 3 days, Or  
Clotrimazole, 500 mg intravaginally, as a single dose, Or  
Fluconazole, 150 mg orally, as a single dose

*Alternative regimen*

Nystatin, 100,000 IU intravaginally, daily for 14 days

*Note:* In men with balanitis or balanoposthitis clotrimazole 1% cream, miconazole 2% cream or nystatin cream 100,000 units/g may be applied twice daily for 7 days.

**Centers for Disease Control:**

Butoconazole, 2% cream, 5 g intravaginally for 3 days. Or  
Butoconazole, 2% cream, 5 g (Butoconazole1-sustained release), single intravaginal application, Or  
Clotrimazole, 1% cream, 5 g intravaginally for 7–14 days, Or  
Clotrimazole, 100 mg, vaginal tablet for 7 days, Or  
Clotrimazole, 100 mg, vaginal tablet, two tablets for 3 days, Or  
Miconazole, 2% cream, 5 g intravaginally for 7 days  
Miconazole, 100 mg, vaginal suppository, one suppository for 7 days, Or  
Miconazole, 200 mg vaginal suppository, one suppository for 3 days, Or  
Miconazole, 1200 mg, vaginal suppository, one suppository for 1 day, Or  
Nystatin, 100,000-unit vaginal tablet, one tablet for 14 days, Or  
Tioconazole, 6.5% ointment, 5 g intravaginally in a single application, Or  
Terconazole, 0.4% cream, 5 g intravaginally for 7 days, Or  
Terconazole, 0.8% cream, 5 g intravaginally for 3 days, Or  
Terconazole, 80 mg, vaginal suppository, one suppository for 3 days

*Oral Agent:*

Fluconazole, 150 mg oral tablet, one tablet in single dose

**European guidelines**

*Induction:* Fluconazole capsule, 150 mg, every 72 hours × 3 doses  
*Maintenance:* Fluconazole capsule, 150 mg, once a week for 6 months

*Alternative Regimens*

*Induction:* Topical imidazole therapy can be increased to 10–14 days according to symptomatic response

*Maintenance:* Clotrimazole pessary, 500 mg, once a week for 6 months

Fluconazole capsule, 50 mg, daily for 6 months  
Itraconazole capsule, 50–100 mg, daily for 6 months  
Ketoconazole capsule, 100 mg, daily for 6 months

**Table 113.19:** Recommendations for the Treatment of Lymphogranuloma Venereum Infection**World Health Organization:**

Doxycycline, 100 mg orally, twice daily for 14 days, Or  
Erythromycin, 500 mg orally, four times daily for 14 days

*Alternative regimen*

Tetracycline, 500 mg orally, four times daily for 14 days

*Note:* Fluctuant lymph nodes (buboes) containing pus should be aspirated through healthy skin. Incision and drainage or excision of nodes may delay healing. Some patients with advanced disease may require treatment for longer than 14 days, and sequelae such as strictures and/or fistulae may require surgery.

**Centers for Disease Control:**

Doxycycline, 100 mg orally, twice a day for 21 days

*Alternative Regimen*

Erythromycin base, 500 mg orally, four times a day for 21 days

**European guidelines**

Doxycycline, 100 mg twice, daily orally for 21 days (or tetracycline 2 g daily Or  
Minocycline, 300 mg, loading dose followed by 200 mg twice daily Or  
Erythromycin, 500 mg, four times daily orally for 21 days.)

*Note:* In pregnant and lactating women, doxycycline, tetracycline, and fluoroquinolones should not be used.

by the development of inguinal and femoral lymphadenitis. Suppuration and abscess formation may occur in affected lymph nodes. Rectal exposure in women or men who have sex with men may lead to proctocolitis. Table 113.19 summarizes the treatment recommendations for LGV.

**Granuloma Inguinale (Donovanosis)**

Granuloma inguinale (Donovanosis) is a genital ulcerative disease caused by the intracellular gram-negative bacterium *Klebsiella granulomatis*. Clinically, patients with donovanosis present with progressive painless genital ulcers usually starting with the appearance of a nodule at the site of infection. Ulcers develop at the site of the nodules. Ulcers are vascular, bleed easily on contact and are beefy-red in appearance. Regional lymph node enlargement typically does not occur. Recommendations for treatment are shown in Table 113.20.

**Chancroid**

Chancroid is caused by *Haemophilus ducreyi*, a gram-negative bacterium that is sexually transmitted. After a short incubation period patients develop painful ulcers at the site of infection and regional lymphadenitis. Suppuration with abscess formation develops in the affected acutely inflamed lymph nodes. Table 113.21 summarizes the treatment recommendations for chancroid.

**Genital Warts**

Genital warts are caused by the human papilloma virus (HPV). They appear as flat, papular or pedunculated growths on the genital area. HPV types 6 or 11 are the common causes of visible warts. However other strains of HPV, high-risk strains that include types 16, 18, 31, 33, and 35, cause cervical carcinoma. In addition

**Table 113.20:** Recommendations for the Treatment of Granuloma Inguinale (Donovanosis)**World Health Organization:**

Azithromycin, 1 g orally on first day, then 500 mg orally, once a day, Or

Doxycycline, 100 mg orally, twice daily

*Alternative regimen*

Erythromycin, 500 mg orally, four times daily, Or

Tetracycline, 500 mg orally, four times daily, Or

Trimethoprim 80 mg/sulfamethoxazole 400 mg, two tablets orally, twice daily for a minimum of 14 days

*Note:* Treatment should be continued until ulcers have healed completely.

**Centers for Disease Control:**

Doxycycline, 100 mg orally, twice a day for at least 3 weeks and until all lesions have completely healed

*Alternative Regimens*

Azithromycin, 1 g orally, once/week, Or

Ciprofloxacin, 750 mg orally, twice a day, Or

Erythromycin base, 500 mg orally, four times a day, Or

Trimethoprim-sulfamethoxazole one double-strength (160 mg/800 mg) tablet orally twice a day

*Note:* Treatment should be continued for at least 3 weeks and until ulcers have healed completely.

*Note:* In pregnant and lactating women, doxycycline, tetracycline, and fluoroquinolones should not be used.

**Table 113.21:** Recommendations for the Treatment of Chancroid**World Health Organization:**

Ciprofloxacin, 500 mg orally, twice daily for 3 days, Or

Erythromycin, 500 mg orally, four times a day for 7 days, Or

Azithromycin, 1 g orally, as a single oral dose

*Alternative regimen*

Ceftriaxone, 250 mg IM, as a single dose

*Note:* No local treatment is needed for lesions—patients should be advised to keep the lesions clean by frequent washing. Fluctuant lymph nodes with pus in them should be aspirated with a needle.

**Centers for Disease Control:**

Azithromycin, 1 g orally, in a single dose, Or

Ceftriaxone, 250 mg intramuscularly (IM) in a single dose, Or

Ciprofloxacin, 500 mg orally, twice a day for 3 days, Or

Erythromycin base, 500 mg orally, three times a day for 7 days

*Note:* Ciprofloxacin is contraindicated for pregnant and lactating women.

*Note:* In pregnant and lactating women, doxycycline, tetracycline, and fluoroquinolones should not be used.

to appearing on the external genitalia, i.e., penis, vulva, scrotum, perineum, and peri-anal skin, genital warts can also occur on the uterine cervix, vagina, urethra, anus, and mouth. Vaccines are available for the prevention of some of the high-risk strains of HPV.

Visible genital warts are treated by physical or chemical removal. Recommendations for treatment are summarized in Table 113.22.

**Scabies**

Scabies is caused by the mite *Sarcoptes scabiei*. Infection is transmitted by direct body contact. In adults this is often

**Table 113.22:** Recommendations for the Treatment of Genital Warts**World Health Organization:***Patient-applied*

Podofilox, 0.5% solution or gel, twice daily for 3 days, followed by 4 days of no treatment, the cycle repeated up to four times (total volume of podofilox should not exceed 0.5 ml/day), Or

Imiquimod, 5% cream applied with a finger at bedtime, left on overnight, three times a week for as long as 16 weeks; wash off 6–10 hr after application

*Note:* The safety of both podofilox and imiquimod during pregnancy has not been established.

*Provider-administered*

Podophyllin, 10–25% in compound tincture of benzoin, applied carefully to the warts once a week; wash off 1–4 hours after each application, Or

Trichloroacetic acid (TCA), 80–90%, applied carefully to the warts each week, avoiding normal tissue, followed by powdering of the treated area with talc or sodium bicarbonate (baking soda) to remove unreacted acid. Repeat application at weekly intervals

*Note:* Some experts advise against the use of podophyllin for anal warts. Large amounts of podophyllin should not be used because it is toxic and easily absorbed. Its use during pregnancy and lactation is contraindicated.

Cryotherapy with liquid nitrogen, solid carbon dioxide, or a cryoprobe, apply every 1–2 weeks, Or  
electrosurgery (electrocautery), Or  
surgical removal

**VAGINAL WARTS**

Cryotherapy with liquid nitrogen, Or

Podophyllin, 10–25%. Allow to dry before removing speculum, Or

Trichloroacetic acid (TCA), 80–90%, applied carefully to the warts each week

**CERVICAL WARTS**

Treatment of cervical warts should not be started until the results from a cervical smear test are known. Most experts advise against the use of podophyllin or TCA for cervical warts—treat patients with cryotherapy, electrocautery, or surgery.

**MEATAL AND URETHRAL WARTS**

Accessible meatal warts may be treated with podophyllin 10–25%, Or podophyllotoxin 0.5%, Or electrosurgical removal

**Centers for Disease Control:***Patient-applied:*

Podofilox 0.5% solution or gel. Patients should apply podofilox solution with a cotton swab, or podofilox gel with a finger, to visible genital warts twice a day for 3 days, followed by 4 days of no therapy. This cycle may be repeated, as necessary, for up to four cycles. Or

Imiquimod 5% cream applied once daily at bedtime, three times a week for up to 16 weeks. The treatment area should be washed with soap and water 6–10 hours after the application.

*Note:* The safety of podofilox and imiquimod during pregnancy has not been established.

*Provider-administered:*

Cryotherapy with liquid nitrogen or cryoprobe. Repeat applications every 1–2 weeks, Or

Podophyllin resin, 10–25%, in a compound tincture of benzoin, applied weekly

*Note:* Do not use if skin is broken and wash off 1–4 hours after applying. The safety of podophyllin in pregnancy is not established. Or

Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA) 80–90%—applied only to the warts and allowed to dry. If an excess amount of acid is applied, the treated area should be powderd with talc, sodium bicarbonate (i.e., baking soda), or liquid soap preparations to remove unreacted acid. This treatment can be repeated weekly, if necessary. Or

Surgical removal either by tangential scissor excision, tangential shave excision, curettage, or electrosurgery

*Alternative Regimens*

Intralesional interferon Or Laser surgery.

through sexual contact, but there are situations in which scabies is transmitted through close body contact not related to sexual activities, such as overcrowded homes and institutions, and bed sharing. For outbreaks of scabies related to non-sexual contact, treatment of all people living in the household or institution is critical. In persons who may have acquired the infestation through sex then sexual partners should also be treated. Adult mites can burrow into the skin within 1 hour. A hypersensitivity reaction develops and this leads to the characteristic symptom of pruritus (itch), usually 2–6 weeks after initial infestation. In reinfestations, the itch may start up soon after infestation occurs.

Pruritus sometimes persists for several weeks after adequate therapy. A single repeat treatment after 1 week may be appropriate if there is no clinical improvement. Additional weekly treatments are warranted only if live mites can be demonstrated. Clothing or bed linen that has possibly been contaminated by the patient in the 2 days prior to the start of treatment should be washed and dried. Treatment recommendations are summarized in Table 113.23.

**Table 113.23:** Recommendations for the Treatment of Scabies**World Health Organization:***Treatment of scabies in adults, adolescents and older children*

Lindane, 1% lotion or cream, applied thinly to all areas of the body from the neck down and washed off thoroughly after 8 hours, Or  
Permethrin cream, 5%, Or

Benzyl benzoate, 25% lotion, applied to the entire body from the neck down, nightly for 2 nights; patients may bathe before reapplying the drug and should bathe 24 hours after the final application, Or  
Crotamiton, 10% lotion, applied to the entire body from the neck down nightly for 2 nights and washed off thoroughly 24 hours after the second application; an extension to 5 nights is necessary in some, Or  
Sulfur, 6% in petrolatum, applied to the entire body from the neck down nightly for 3 nights; patients may bathe before reapplying the product and should bathe 24 hours after the final application.

*Note:* Lindane is not recommended for pregnant or lactating women.

*Treatment of scabies in infants, children under 10 years of age, pregnant or lactating women*

Crotamiton, 10%, as above, Or  
Sulfur, 6%, as above, Or  
Permethrin, 5% cream, applied in the same way as the sulfur regimen described above.

*Note:* Sexual contacts and all household contacts should be treated as above.

**Centers for Disease Control:**

Permethrin cream (5%) applied to all areas of the body and washed off after 8–14 hours, Or

Ivermectin 200 µg/kg orally, repeated in 2 weeks

*Alternative Regimens*

Lindane (1%) 1 oz. of lotion or 30 g of cream applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after 8 hours

*Note:* Infants, young children, and pregnant or lactating women should not be treated with lindane. They can be treated with permethrin. Ivermectin is not recommended for pregnant or lactating patients. The safety of ivermectin in children who weigh <15 kg has not been determined.



## Phthiriasis (Pediculosis Pubis; Pubic Lice)

The louse, *Pthirus pubis*, is the cause of pediculosis pubis (pubic lice). The infestation is usually transmitted by sexual contact. Patients usually seek medical care because of pruritus. Treatment recommendations are summarized in Table 113.24.

**Table 113.24:** Recommendations for the Treatment of Phthiriasis (Pediculosis Pubis; Pubic Lice)

### World Health Organization:

#### Recommended regimens

Lindane, 1% lotion or cream, rubbed gently but thoroughly into the infested area and adjacent hairy areas and washed off after 8 hours; as an alternative, lindane 1% shampoo, applied for 4 minutes and then thoroughly washed off, Or

Pyrethrins plus piperonyl butoxide, applied to the infested and adjacent hairy areas and washed off after 10 minutes; retreatment is indicated after 7 days if lice are found or nits are observed at the hair-skin junction. Clothing or bed linen that may have been contaminated by the patient in the 2 days prior to the start of treatment should be washed and dried well, or dry-cleaned, Or  
Permethrin 1%, as above

*Note:* Lindane is not recommended for pregnant or lactating women.

### Centers for Disease Control:

Permethrin, 1% cream rinse applied to affected areas and washed off after 10 minutes, Or

Pyrethrins with piperonyl butoxide applied to the affected area and washed off after 10 minutes

#### Alternative Regimens

Malathion, 0.5%, lotion applied for 8–12 hours and washed off, Or  
Ivermectin, 250 µg/kg, repeated in 2 weeks

## Summary

The importance of establishing standardized guidelines for the management of STIs nationally cannot be over-emphasized. The development of such guidelines requires inputs from laboratory specialists, epidemiologists, national essential drug programs as well as clinicians and pharmacists.

When selecting appropriate drugs for the treatment of STIs consideration should be given to the efficacy of the recommended drugs, and their safety and ease of administration. The cost of drugs is also an important consideration especially in resource constrained settings. However, it is probably more cost effective to use more costly drugs that are more effective at the first point of contact a patient makes with a health facility than using cheaper drugs that are less effective as treatment failures result in further transmission of infection, and increase the risk of the development of complications of infection and in selecting drug-resistant strains of pathogens.

In this chapter, a review of recommendations made by the World Health Organization, the Centers for Disease Control, and the European Union is provided.

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# Guidelines for the Treatment of HIV in Industrialized and Middle Income Countries—Adults, Adolescents, and Pediatric

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To date, a cure for HIV has remained elusive, largely due to the inability to eradicate latent infection of host reservoirs of CD4 cells early in the course of disease.<sup>1</sup> Antiretroviral therapy, therefore, is primarily aimed at maximum suppression of viral replication, which has been shown to prevent progression to AIDS and reduce morbidity and mortality by restoring immunological function.<sup>2,3</sup> The use of combination antiretroviral therapy is associated with durable virological suppression, which also limits the emergence of resistant viral strains.

Viral suppression also serves to curb the HIV epidemic by reducing transmission and increasingly the benefits of viral suppression on “non-AIDS” events have become apparent. The Strategies for Management of Antiretroviral Therapy (SMART) group performed a randomized trial of 5472 participants whose baseline CD4 count was greater than 350 cells/mm<sup>3</sup>.<sup>4</sup> Patients were assigned to “drug conservation” (DC)—use of antiretroviral therapy (ART) only when their CD4 count was less than 250 cells/μL and continued until the count rose above 350 cells/μL, when it was stopped again; or to “virological suppression” (VS) where the ART was uninterrupted once initiated. Perhaps not surprisingly, the DC group had a significantly increased risk of opportunistic disease or all cause mortality (HR 2.6, 95% CI 1.9–3.7;  $p < 0.001$ ) but only 8% of deaths were due to opportunistic disease and unexpectedly, the DC group had more cardiovascular, renal, and hepatic disease (HR 1.7, 95% CI 1.1–2.5;  $p = 0.009$ ) despite being exposed to less ART, which had previously been thought to be a major contributor to these “non-AIDS” events.

This landmark trial has provided clear evidence that once started, ART should generally be continued indefinitely as the risks of uncontrolled HIV viremia outweigh the potential risks of drug toxicity.<sup>5</sup> With the emphasis on lifelong treatment now, the decision of when to start ART has become even more important.

## When to Treat?

### ASYMPTOMATIC PATIENTS

The era of antiretroviral therapy began in 1987 with the introduction of the first nucleoside reverse transcriptase inhibitor (NRTI), zidovudine (AZT) that was used initially to treat patients with severe immunosuppression (CD4 counts less than 200 cells/μL) or opportunistic illness.<sup>6</sup> It soon became apparent that the use of zidovudine monotherapy in patients, not at immediate risk of disease progression or death, was not beneficial in the long term<sup>7–11</sup> with the rapid development of resistance and lack of any survival benefit. Dual NRTI therapy with AZT and didanosine (ddI) or zalcitabine (ddC) followed,<sup>9,12,13</sup> but still quickly selected for resistant viral strains.<sup>14,15</sup>

The introduction of highly active antiretroviral therapy (HAART or more simply cART) in 1996 revolutionized the management of HIV.<sup>3,16</sup> Combination ART (cART) involves the use of three antiretroviral drugs from at least two different classes and was shown to effectively provide durable virological suppression and the development of protease inhibitors in 1995 appeared to confer an additional benefit on survival when used as part of cART<sup>2,3,10,16</sup> likely attributable to their potency and high barrier to resistance when ritonavir boosted.<sup>17</sup>

It became evident that the initial hope of viral eradication was not attainable due to infection of latent T-cell reservoirs,<sup>18,19</sup> but virological suppression was demonstrated to have many other benefits—allowing restoration of the T-cell count and immune responses against infections such as *Pneumocystis jirovecii* (PCP), *Mycobacterium avium* complex (MAC), and cytomegalovirus (CMV). This translated into dramatically improved survival and reduced incidence of opportunistic infections and AIDS events.<sup>2,3</sup>

Despite the success of cART, there were negative aspects to treatment. Pill burden in the early years of antiretroviral therapy was a major hindrance with some regimens requiring patients

to take 6–8 tablets three times per day. Side effects were also considerable ranging from severe diarrhoea or skin rash, to long-term side effects of lipodystrophy, diabetes, and peripheral neuropathy. Compliance and medication toxicity became the major issues facing HIV management and with the limited number of drug options, it was clear that a treatment threshold had to be established.

In patients not yet on cART, a higher HIV viral load is associated with more rapid HIV disease progression independent of CD4 cell count.<sup>20,21</sup> However, in patients commencing cART, CD4 cell count is more important than HIV viral load in determining the need for treatment.<sup>22</sup> The risk of AIDS events and death clearly increases with falling CD4 cell count.<sup>23,24</sup> A number of randomized trials have demonstrated that there is a clear benefit to ART below a CD4 count of 200 cells/ $\mu$ L.<sup>25–27</sup> Opportunistic infections, non-AIDS events, and death are all reduced substantially with initiation below this CD4 count level.<sup>22,28</sup> A number of large observational cohort studies have also shown similar benefits.<sup>29,30</sup>

There is also some evidence for the benefit of ART above a CD4 count of 200 cells/ $\mu$ L. A study of 816 HIV-positive patients with CD4 counts of between 200 and 350 cells/ $\mu$ L was undertaken in Haiti. Participants were randomized to an open label trial of ART within 2 weeks, compared with standard of care, waiting for a CD4 count less than 200 cells/ $\mu$ L or symptomatic illness.<sup>31</sup> The study showed a higher mortality (HR 4.0,  $p = 0.001$ ) and high incidence of tuberculosis (HR 2.0,  $p = 0.01$ ) if ART was delayed until a CD4 count of 200 cells/ $\mu$ L or less, although this study was perhaps not directly comparable to first world nations.

Controversy currently exists now over the benefits of treatment initiation above 500 cells/ $\mu$ L. There are a number of arguments in favor of earlier treatment. It has been suggested that an individual's CD4 response to cART may be linked to their nadir CD4 count,<sup>32,33</sup> hence earlier antiretroviral treatment would allow patients to sustain far greater periods of good immune function than if therapy had been delayed.<sup>34</sup> There have been some conflicting studies with regards to this theory<sup>35</sup> and it remains unproven if earlier cART would provide a benefit in this regard. Non-AIDS events such as cardiovascular disease, liver disease, and malignancies may be associated with HIV viral replication<sup>36–39</sup> and certainly the SMART study demonstrated a lower rate of cardiovascular events in the group on continuous ART when compared with patients interrupting therapy.<sup>4</sup> From a public health perspective, earlier treatment of HIV may limit the transmission of the virus and act to curb the rate of new infections.<sup>16,40</sup>

The current debate centres around evidence from the analysis of two retrospective cohort studies—the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) study<sup>41</sup> and the Antiretroviral Therapy Cohort Collaboration (ARTCC)<sup>30</sup> that have provided somewhat different results.

The NA-ACCORD study<sup>41</sup> performed two parallel analyses across their cohort; the first of which compared the rates of all cause mortality in patients initiating ART for the first time with

a CD4 count of 351–500 cells/ $\mu$ L to those with a CD4 count 350 cells/ $\mu$ L or less. Of 8362 patients, 25% initiated ART within the CD4 range of interest and were found to have a relative risk of death of 1.69 (95% CI 1.25–2.26;  $p < 0.001$ ). This risk reduced slightly when adjusted for intravenous drug use among patients and became non-significant statistically (RR 1.28; 95% CI 0.85–1.93;  $p = 0.23$ ). The second analysis was performed in patients starting ART with a CD4 count of greater than 500 cells/ $\mu$ L compared with those starting below this level. A total of 9155 patients were used in this analysis, of which 24% started ART at a CD4 count above 500 cells/ $\mu$ L. A relative risk of death of 1.94 (95% CI 1.37–2.79;  $p = 0.006$ ) was seen in the group who deferred initiation of ART and the risk remained similar when accounting for intravenous drug use (RR 2.00; 95% CI 1.15–3.46;  $p = 0.001$ ) in this analysis. Unsurprisingly, where cause of death was identified, the majority of deaths were due to non-AIDS events in both analyses.

The ARTCC study evaluated the combined endpoint of AIDS events and death from any cause in over 45,000 patients from North America and Europe from both before and after the introduction of cART. Deferring treatment until a CD4 count of 251–350 cells/ $\mu$ L, as compared with commencing at a CD4 of 351–450 cells/ $\mu$ L, was associated with an increased risk of AIDS (HR 1.28, 95% CI 1.04–1.57). In contrast to the NA-ACCORD data, at CD4 count ranges greater than 450 cells/ $\mu$ L the hazard ratios benefit of initiating cART became statistically non-significant.

While both studies appear to show benefits of earlier antiretroviral therapy, albeit at somewhat differing thresholds, these increased relative risks translate into only a small number of actual events. Neither study looked at non-fatal non-AIDS events that are likely to be more common than AIDS events at higher CD4 counts<sup>27,42</sup>—although there is some evidence that these too may be reduced by treatment of HIV.<sup>4,39</sup> Both studies used sophisticated statistical methods to try and adjust for confounders, including intravenous drug use and lead time bias, but inevitably residual confounders will persist and will remain a major limitation to the interpretation of their results.

To date the only randomized data for the benefit of earlier ART in patients with CD4 counts greater than 350 cells/ $\mu$ L exists in the form of a subset analysis of the Strategies for Management of Antiretroviral Therapy (SMART) study comprising of 477 patients off ART at enrolment into the study (52% were ART naive).<sup>43</sup> Within the confines of this post-hoc analysis, delaying ART until CD4 counts fell below less than 250 cells/ $\mu$ L, was associated with an increased risk of AIDS or death (HR 3.47, 95% CI 1.26–9.56,  $p = 0.02$ ) and non-AIDS events (HR 7.02, 95% CI 1.57–31.38) when compared with starting above a CD4 count of 350 cells/ $\mu$ L. These patients, however, were not randomized with the intent of what CD4 threshold to start ART and as such this study does not truly answer the original question. Ultimately a randomized controlled trial is required to answer this question. The Strategic Timing of Antiretroviral Treatment (START) trial is enrolling patients with a CD4 count above 500



cells/ $\mu$ L and randomizing them to begin ART immediately or defer until the CD4 count has fallen to 350 cells/ $\mu$ L. This study will provide some of the best evidence for the timing of ART initiation; however, the completion of the trial, and therefore the trial results, will likely be some years away.

Unsurprisingly given this debate, current guidelines across the world differ in their recommendations as to the optimal timing of ART. The US DHHS panel<sup>44</sup> agreed strongly that ART should be given at CD4 counts less than 350 cells/ $\mu$ L but also recommend treatment at counts between 350 and 500 cells/ $\mu$ L, although the panel was split on the strength of this recommendation. Above 500 CD4 cells the panel was again divided in opinion with 50% recommending ART and 50% considering it optional. Despite this the San Francisco HIV treatment policy is now one of “test and treat”<sup>45</sup> and only time will tell if this decision was justified or perhaps premature. The European Clinical AIDS Society (EACS) antiretroviral treatment guidelines<sup>46</sup> are similar to the DHHS in their guidelines for CD4 counts below 350 cells/ $\mu$ L. Between 350 and 500 CD4 cells, treatment is recommended in those with hepatitis co-infection, high cardiovascular risk, malignancy, high viral load or rapid CD4 decline and in women who are pregnant. They do not however recommend ART at CD4 levels greater than 500 cells/ $\mu$ L.

In light of such controversy, and while awaiting the results of the START trial, the decision to start ART in an asymptomatic patient with a CD4 count of greater than 350 cells/ $\mu$ L is very much one that needs to be made on an individual patient basis. Given the results provided by the SMART study,<sup>4</sup> definitively demonstrating that once started, continuous ART without interruption reduces mortality and, unexpectedly, non-AIDS events—the decision to start a patient on ART is not one to be taken lightly. Important considerations must include the need for compliance to prevent development of viral resistance, drug toxicities, quality of life, pill burden, and also medical comorbidities such as hepatitis co-infection and pregnancy (see below). Costs, both to patient and healthcare system also need to be factored. Ultimately, an informed discussion with each individual patient regarding the benefits and risks of early ART is needed.

## ACUTE OPPORTUNISTIC INFECTION

Opportunistic infections (OI) occur at states of profound immunosuppression so it would seem logical that ART would be beneficial in this setting. Where no or limited effective medical therapy exists other than presence of an intact immune system this is certainly the case, for example progressive multifocal leukoencephalopathy (PML), cryptosporidiosis, and microsporidiosis.<sup>47–49</sup> However, in the setting of an acute OI with effective medical treatment the timing of ART initiation may vary.

ART leads to recovery of the host immune system and pathogen-specific immunological responses thereby improving treatment efficacy of the original OI while also acting to prevent further OIs from developing. However, concerns that severely

ill patients may not tolerate ART in the setting of acute illness and the potential for drug interactions and overlapping toxicities detrimental to the patient have resulted in delayed initiation of ART in this setting. Immune reconstitution inflammatory syndrome (IRIS) is also a common concern,<sup>28,50</sup> and may actually cause clinical deterioration and it is for this reason some experts recommend delaying ART initiation until the completion of the OI therapy.

For some OIs, such as PCP, the benefits of early ART are clear. Zolopa et al.<sup>28</sup> randomized 282 patients with a variety of OIs to “early ART”, defined as treatment within 14 days of diagnosis (median 12 days), versus “deferred ART”, defined as after completion of treatment for the OI (median 45 days) (ACTG 5164). The predominant OIs in the study were *Pneumocystis jirovecii* pneumonia (63%) with cryptococcal meningitis (12%) the next most common diagnosis. The early ART group had fewer AIDS progression/deaths (OR 0.51, 95% CI 0.27–0.94) and longer time to progression to AIDS or death (HR 0.53; 95% CI 0.30–0.92). IRIS occurred in 7.6% of patients at a median of 33 days on ART, and there was no difference in rates of IRIS whether treatment was started late or early. The use of corticosteroids (in 70% of patients with PCP) delayed but did not prevent the occurrence of IRIS. Previous concerns regarding an increased rate of adverse effects from overlapping medication toxicity were not seen in the study.

Timing of ART initiation in other OIs is less clear. With regards to pulmonary tuberculosis and HIV, the SAPIT study<sup>51</sup> from South Africa examined over 600 patients with new diagnosis of both pulmonary tuberculosis and HIV and randomized them to one of three treatment arms. The first group were started on ART at the completion of tuberculosis treatment (sequential therapy), the remaining two groups received their HIV treatment during their tuberculosis treatment (integrated therapy)—either early (within 4 weeks) or late (within 4 weeks of the completion phase of the intensive phase of tuberculosis treatment—i.e., at 2 months). The combined integrated therapy arms, when compared against the sequential group, were clearly associated with a lower mortality rate (5.4 per 100 person years versus 12.1 per 100 person years; HR 0.44; 95% CI 0.25–0.79,  $p=0.003$ ) with no difference in the rate of adverse events although IRIS was more common in the integrated treatment group. This result led to early termination of the sequential arm by the data safety monitoring board (DSMB) and the study continued with only the two integrated groups.

Thirty-five patients with cryptococcal meningitis (CM) were included in the ACTG 5164 study described above, and there was no difference in the incidence of IRIS or mortality,<sup>28</sup> but a more recent prospective randomized study suggested that ART given very early in the treatment course of cryptococcal meningitis may in fact be detrimental. A Zimbabwean study of CM<sup>52</sup> randomized 54 patients to either “early ART” (within 72 hours) or “delayed ART” (after 10 weeks of fluconazole therapy). These patients were severely immunocompromised with a median CD4 count of 37 cells/ $\mu$ L; however, the 3 year mortality rate

was significantly better in the delayed ART group (88% vs. 54%,  $p < 0.006$ ) equating to almost a three times greater risk of death with early ART. The majority of these deaths were due to CM itself and occurred within 4 weeks of starting treatment suggesting that IRIS may have had a significant contribution.

Other retrospective studies of ART initiation in tuberculosis<sup>53</sup> and severe PCP<sup>54</sup> also show a clear survival benefit of early ART although once again there is no consensus as to the exact timing. The overall evidence is that for patients with acute OIs for which medical treatment exists should receive early ART, starting during the treatment of their OI, but exactly how early is a question that remains unanswered.<sup>49</sup> In the absence of controlled evidence it seems prudent to establish the patient on primary treatment for their OI ensuring they tolerate this and do not suffer adverse effects, and then start ART soon after<sup>49</sup>—perhaps earlier in PCP than in CM where the consequences of IRIS can be more devastating.

## Individual Drugs and Side Effects

The number of antiretroviral drugs has expanded rapidly since their advent in 1987, starting with a couple of drugs within a single class, to the current state in 2010 of 15 drugs across six different classes. ART development has been unique in that different classes of agents which have been developed to target specific processes within the HIV lifecycle (see Chapter 66, “Human Immunodeficiency Virus: Biology and Natural History of Infection”), such that combination therapy involving at least two different classes limits the development of resistance.<sup>2,3,10,16</sup>

### NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

The first class of ART developed was the nucleoside reverse transcriptase inhibitors (NRTIs) and began with the introduction of zidovudine (AZT) in 1987.<sup>55</sup> NRTIs competitively inhibit the viral reverse transcriptase enzyme (RNA-dependent DNA polymerase) that facilitates viral RNA transcription into a complete DNA molecule. As nucleoside/nucleotide analogs, they are incorporated by reverse transcriptase into the newly formed DNA but prevent chain elongation thereafter, thereby terminating the process. They include nucleoside analogs—zidovudine (AZT), didanosine (ddI), stavudine (d4T), lamivudine (3TC), emtricitabine (FTC), zalcitabine (ddC), and abacavir (ABC)—or the single nucleotide analogue—tenofovir (TDF). In addition to HIV DNA polymerase, humans also have a number of their own DNA polymerases, specifically  $\beta$  and  $\gamma$ , which are also inhibited by NRTIs and interfere with ATP and mitochondrial enzyme production, leading to mitochondrial toxicity and increased lactate production. Clinically, this can manifest as myopathy, peripheral neuropathy, pancreatitis, and lactic acidosis.

Peripheral neuropathy associated with NRTIs is particularly seen with the older agents in the class—stavudine, zalcitabine, and didanosine—in up to 30% of patients treated with these agents.<sup>56</sup> Classically, the neuropathy presents relatively acutely with a painful, distal, sensory neuropathy that may improve

after drug cessation, albeit sometimes after a brief progression of symptoms.<sup>57</sup> Unlike HIV-associated peripheral neuropathy, NRTI-associated neuropathy often occurs in the setting of suppressed viral replication. Given the frequency of this complication developing, these NRTIs are now rarely used in the modern cART era.

Lipodystrophy, first described in 1998,<sup>58</sup> is a condition seen commonly in HIV and while it can be seen in antiretroviral naive patients, it is more often seen as a complication of cART.<sup>59</sup> While there is no formal consensus definition, it encompasses both peripheral lipodystrophy (loss of fat on limbs and face) associated with NRTI and NNRTI (specifically efavirenz) use,<sup>60,61</sup> and central lipohypertrophy (central obesity, visceral fat, and buffalo humps) often seen with protease inhibitor (PI) use.<sup>62</sup> Patients frequently have associated metabolic derangement including insulin resistance and dyslipidemia with resultant increase in cardiovascular risk.<sup>62</sup> Within the NRTI class, the thymidine analogs (zidovudine and stavudine) have the greatest association with lipodystrophy and tenofovir, abacavir and lamivudine the least.<sup>62</sup> However it is the cosmetic consequences that can be extremely distressing to patients, compounded by the lack of effective treatment options available for this condition. Changing the offending antiretroviral to another agent leads to some improvement in subcutaneous fat mass,<sup>63–65</sup> but in general, fat changes are slow to improve and cosmetic surgery may provide some benefit.<sup>60</sup>

Some specific drug side effects are listed in Table 114.1. Of particular note, abacavir has the potential to cause a serious hypersensitivity reaction, classically occurring after approximately 1–2 weeks of treatment and presenting with fever, rash, and abnormal liver function. This reaction could be potentially fatal, especially on re-exposure to ABC. In 2008, the HLA B57\*01 genotype, found in 5.6% of a study population, was found to significantly predict immunologically confirmed reactions with a negative predictive value of 100% and a positive predictive value of 47.9%.<sup>66</sup> This test is now considered mandatory prior to consideration of ABC use in treatment guidelines.<sup>44,67</sup>

### NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

As the name suggests, non-nucleoside reverse transcriptase inhibitors (NNRTIs) also inhibit viral reverse transcriptase, but they do so by actually interfering with the enzyme's activity rather than by being incorporated into the viral DNA particle. They are divided into the first generation NNRTIs—delavirdine, which is rarely used in modern practice, nevirapine (NVP), and efavirenz (EFV)—and the newer second generation NNRTIs—etravirine (ETV) and rilpivirine (TMC278).

Class side effects of the NNRTIs include rash, which is relatively common with all members of the NNRTI group although there is only minor cross-reactivity between the individual drugs, i.e., rash to one agent does not predict the development of rash with another NNRTI (Table 114.2). All drugs in this class are metabolized by cytochrome P450 3A4 enzymes and variably induce or inhibit the same enzymes making drug interactions an important consideration

**Table 114.1:** Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

NRTI	Dosing	Common side effects	Less common side effects	Other features
Zidovudine (AZT)	250 mg BD	Bone marrow suppression—esp. anemia Gastrointestinal upset Lipoatrophy	Lactic acidosis Myopathy	Prevention of mother-to-child transmission
Lamivudine (3TC)	150 mg BD OR 300 mg daily	Well tolerated	Headache	Hepatitis B activity
Emtricitabine (FTC)	200 mg daily	Well tolerated	Rash	Hepatitis B activity
Didanosine (ddI)	250 mg daily if <60 kg OR 400 mg daily if >60 kg	Peripheral neuropathy Gastrointestinal upset	Pancreatitis Lactic acidosis	Overlapping toxicity—so should not be used together
Stavudine (d4T)	30 mg daily if <60 kg OR 40 mg daily if >60 kg	Peripheral neuropathy Lipoatrophy*	Pancreatitis Lactic acidosis	
Abacavir (ABC)	600 mg daily	Well tolerated	Hypersensitivity reaction*	*Almost all patients who develop hypersensitivity are HLA-B57*01 positive—therefore screening recommended prior to commencement
Tenofovir (TDF)	300 mg daily	Well tolerated	Renal impairment and/or Fanconi's syndrome	Hepatitis B activity

\*Lipoatrophy can occur with all the NRTIs but is more commonly seen with stavudine and zidovudine.

when they are used. Interactions occur with all members of the class but to varying degrees; delavirdine is an inhibitor of CYP450 3A4, nevirapine is an inducer of the same enzyme, and efavirenz both inhibits and induces 3A4. As a class the NNRTIs also generally have a low genetic barrier to resistance which can lead to early resistance in the setting of poor adherence.

Another idiosyncrasy to NNRTIs is their extremely long half-life. This needs to be considered when they are used as part of combination therapy—ceasing all three drugs simultaneously will in fact result in NNRTI monotherapy for 1–2 weeks which can inadvertently lead to NNRTI resistance rapidly. Techniques to avoid this include a staggered cessation of ART, i.e., NNRTI first and continue the two (or more) other agents for 5–7 days before ceasing all together; or alternatively switch the NNRTI to a PI and continue this treatment for up to a month before ceasing all together.<sup>68</sup>

Nevirapine may induce a potentially fatal hypersensitivity reaction in individuals, primarily consisting of the development of a rash and hepatitis. This side effect was later found to be fairly predictable by the patient CD4 count at initiation of treatment. Men with a CD4 count greater than 400 cells/ $\mu$ L and women with a CD4 count greater than 250 cells/ $\mu$ L are at significantly higher risk of developing this toxicity.<sup>69</sup> The severity of this hypersensitivity reaction cannot be understated and absolutely contradicts future use of nevirapine.

Efavirenz has now become one of the mainstays of primary ART for a number of reasons. It is fairly well-tolerated—the most common side effect being that of central nervous system toxicity. For the majority of patients this may consist of vivid dreams, some sleep disturbance, dizziness or difficulty in concentrating. In a small percentage of patients, EFV may actually potentiate psychiatric illness and as such it is not recommended in patients with current psychiatric disease or severe past psychiatric illness.

**Table 114.2:** Non-nucleoside Reverse Transcriptase Inhibitors

NRTI	Dosing	Common side effects	Less common side effects	Other features
Nevirapine (NVP)	200 mg daily for 14 days then increase to 200 mg BD	Rash Abnormal LFTs	Steven-Johnson syndrome Hepatitis	Induces its own metabolism—explaining the unusual dosing schedule when initiating
Delavirdine (DLV)	400 mg TDS	Rash Hepatic transaminitis		Gastric acid lowering drugs inhibit DLV absorption
Efavirenz (EFV)	600 mg daily	Rash—can treat through unless worsening or concurrent hepatitis Central nervous system side effects	Severe depression—possibly leading to suicidality	Dyslipidemia Lipodystrophy
Etravirine (ETV)	200 mg BD	Rash—may resolve with continued use	Hypersensitivity reaction Nausea	



Etravirine was licensed in 2008 and became the first “second” generation NNRTI with activity against some, but not all, NNRTI-resistant viruses in patients who have previously failed an older NNRTI regimen.<sup>70</sup> In fact there are a number of mutations in the viral reverse transcriptase associated with ETV resistance and there appears to be a cumulative effect of these mutations on the efficacy of ETV.<sup>71</sup>

The phase 3 DUET studies examined the use of etravirine in treatment-experienced patients with known NNRTI resistance. All patients received a background regimen including boosted darunavir, NRTIs, with or without enfuvirtide. By 96 weeks significantly more patients who received etravirine, compared with placebo, achieved a viral load of less than 50 copies/mL (57% vs. 36%,  $p < 0.0001$ ).<sup>70</sup> Adverse events were similar between groups except for the incidence of rash (21% vs. 12%,  $p < 0.0001$ ).

## PROTEASE INHIBITORS

After integration into the host genome, HIV is transcribed into an RNA polyprotein consisting of Gag and Pol proteins, which requires cleavage by viral protease to make smaller, complete HIV virions. Protease inhibitors (PIs) prevent this cleavage with the consequent production of viral RNA in a non-infectious form.

PIs are all metabolized by the cytochrome P450 3A4 enzyme and this mechanism is exploited therapeutically with the use of ritonavir “boosting”. Ritonavir (RTV) is a PI with anti-HIV activity, but significant side effects are seen—primarily gastrointestinal disturbance and lipid abnormalities at doses required to achieve a therapeutic effect.<sup>72</sup> Ritonavir however also

inhibits the CYP 3A4 enzyme, preventing the clearance of drugs metabolized by this mechanism and hence increasing drug levels and half lives substantially. This boosting phenomenon occurs with quite small doses of RTV and allows for a lower dose of the concomitant PI to be administered—often as a single daily or twice daily dose. Boosting also reduces the risk of development of resistance by ensuring adequate drug levels of the primary PI. In general, most PIs are recommended for use with RTV boosting (often abbreviated as “/r”), especially when used for patients who are antiretroviral experienced and have developed some PI resistance mutations already.<sup>17</sup> Atazanavir (ATV) can be used without RTV but requires a larger dose (400 mg) in this scenario and may not be as effective in combination with some other antiretrovirals, such as with tenofovir-emtricitabine.<sup>73</sup>

As a group the PIs are all associated with dyslipidemia to varying degrees although atazanavir and darunavir tend to be more lipid friendly in comparison with older agents. Other class side effects appear to be an increased risk of hyperglycemia, lipodystrophy (see above), and a possible association with an increased risk of bleeding in hemophiliac patients.<sup>44</sup> Gastrointestinal disturbance is also common with all PIs including nausea, abdominal pain, and diarrhea—these symptoms are all somewhat exacerbated by the concomitant use of ritonavir boosting. Specific side effects are listed in Table 114.3.

## CCR5 CO-RECEPTOR ANTAGONISTS

Binding to CD4 receptors, the HIV virus requires attachment to a co-receptor to infect a host cell. Most commonly, this co-receptor is the CCR5 chemokine receptor, especially in early infection.

**Table 114.3:** Protease Inhibitors

PI	Dosing (PI/ritonavir)	Common side effects	Less common side effects	Other features
Indinavir (IDV)	800 mg/100 mg BD OR 800 mg/200 mg BD OR 400 mg/400 mg BD	Nephrolithiasis Gastrointestinal adverse effects	Nephrolithiasis Nephrotoxicity	
Saquinavir (SQV)	1600 mg/100 mg daily (soft gel cap) OR 400 mg/100 mg BD (hard gel cap)	Gastrointestinal adverse effects Lipodystrophy	Hepatitis	
Atazanavir (ATV)	300 mg/100 mg daily OR 400 mg daily (without RTV)	Hyperbilirubinemia	Nephrolithiasis	Good lipid profile
Lopinavir (LPV)	400 mg/100 mg BD	Gastrointestinal adverse effects esp. diarrhea		Dyslipidemia particularly an issue
Darunavir (DRV)	800 mg/100 mg daily in treatment naïve patients OR 600 mg/100 mg twice daily in treatment experienced patients	Well tolerated	Rash	Good lipid profile
Tipranavir (TPV)	500 mg/200 mg BD	Gastrointestinal adverse effects Hyperlipidemia	Rash Intracranial hemorrhage	
Fosamprenavir (FPV)	1400 mg/200 mg daily OR 700 mg/ 100 mg BD in treatment naïve patients OR 700 mg/100 mg BD in treatment experienced patients	Gastrointestinal upset Rash	Nephrolithiasis	

Alternatively, and more commonly with patients infected for a number of years, HIV may use the CXCR4 receptor or both CCR5 and CXCR4, known as dual-tropic virus. However, primary infection with X4 virus alone remains uncommon.<sup>74</sup>

Maraviroc (MVC) is currently the only marketed CCR5 antagonist. The initial studies of MVC in treatment-experienced patients, MOTIVATE 1 and 2, randomized a total of 1049 patients to one of the three arms, once or twice daily maraviroc and placebo, with an optimized background treatment (OBT) regimen<sup>75</sup>—generally defined in HIV trials as the combination of antiretrovirals, dictated by resistance testing, that is likely to retain the most activity against each individual's virus. Approximately 44% of patients screened for the study still had R5 tropic virus despite triple antiretroviral class treatment experience. At week 48, patients receiving maraviroc had a greater mean reduction in HIV viral load and more often had a viral load of less than 50 copies/mL (once daily maraviroc 42% and twice daily maraviroc 47% compared with placebo 16% in MOTIVATE 1; 45% in both maraviroc arms compared with 18% placebo in MOTIVATE 2. Maraviroc was also associated with a greater CD4 cell increase. These benefits have been shown to be durable out to 96 weeks.<sup>76</sup> It is possible that even more patients could achieve virological suppression with the concomitant use of newer antiretrovirals, such as darunavir, etravirine, and raltegravir that were not allowed within the MOTIVATE studies' protocol.<sup>75</sup>

The MERIT study subsequently followed and compared maraviroc twice daily against efavirenz both with an NRTI backbone of lamivudine-zidovudine.<sup>77</sup> All patients entering the study had R5 tropic virus as determined by original Trofile assay. The initial intention to treat (ITT) analysis compared a total of 721 patients and although a larger CD4 cell count increase was seen in the maraviroc arm, by week 48 the proportion of patients who achieved a viral load of less than 50 copies/mL was 65.3% with maraviroc compared with 69.3% with efavirenz. This result failed to reach predetermined non-inferiority criteria and the discrepancy was even higher in patients with viral loads greater than 100,000 copies/mL (59.6% vs. 66.6%). A newer Trofile assay, much more sensitive to lower proportions of X4 virus was subsequently developed and samples from the MERIT study were reanalyzed—14.7% of the original study population were found to have dual tropic virus. Using an ITT analysis with patients with R5 virus only, as per the new assay, demonstrated that maraviroc was indeed non-inferior to efavirenz in virological suppression at week 48 (68.5% vs. 68.3%).<sup>74</sup>

After initial concern over cardiac QT interval prolongation, MVC was shown to be safe at current therapeutic doses and is generally well-tolerated. Dosing can be confusing due to a number of drug interactions, and therefore the dose of MVC may need to be increased or decreased according to concomitant medications.

## FUSION INHIBITORS

The sole agent within this class is enfuvirtide (T20). T20 acts by inhibiting the HIV gp41 protein that prevents an HIV virion

from fusing with a host cell membrane. This unique mechanism of action allows T20 to have efficacy even in patients heavily experienced with other classes of ART, in the context of a combination antiretroviral therapy.

The TORO study<sup>78</sup> was performed in treatment-experienced patients who were randomized to OBT with and without the addition of T20. At 48 weeks, 30.4% of patients receiving T20 were virally suppressed below 400 copies/mL and 18.3% below 50 copies/mL, as compared with 12.0% and 7.8% who received OBT alone. A large number of patients on OBT failed therapy were switched to the T20 arm during the study. By 96 weeks, of those patients receiving T20 who completed the study, 26.5% had a viral load of less than 400 copies/mL and 17.5% were having less than 50 copies/mL.<sup>79</sup> Patients who retained activity to lopinavir/ritonavir, a new boosted PI at the time of the study, had improved efficacy compared with those who had previously been treated with it.<sup>78</sup> This would suggest that in patients with significant treatment experience but who still retained some activity from newer PIs (e.g., darunavir and lopinavir) would achieve better efficacy than the numbers stated above—especially if combined with newer antiretrovirals, such as raltegravir, etravirine, and maraviroc.

The main shortfall of T20 is its mode of administration. Subcutaneous injections, twice daily, which result in injection site reactions in the majority (>95%) of patients are a significant deterrent to its uptake and result in discontinuation in 7–10% of patients in the short term,<sup>79</sup> but it is otherwise well-tolerated.<sup>80</sup>

## INTEGRASE STRAND INHIBITORS (INSTI)

Integrase inhibitors are the latest class of ART developed and have revolutionized salvage therapy as well as providing a new option in the treatment of treatment naive patients. Integrase is a viral enzyme that allows HIV DNA, formed by reverse transcription, to be inserted into the host genome. Integrase inhibitors inhibit the viral integrase enzyme, prohibiting viral integration and as this enzyme is a novel target in antiretroviral therapy, integrase inhibitors will generally have activity against viruses that have failed other classes of ARVs in the past.<sup>81</sup> Raltegravir is the first marketed INSTI but a number of others are likely to follow in coming years.

BENCHMRK 1 and 2 were randomized, placebo-controlled trials involving 699 patients with triple-class antiretroviral resistance who received OBT with raltegravir or placebo. At week 48, 62.1% of patients receiving raltegravir achieved a viral load of less than 50 copies/mL, as compared with the placebo group where only 32.9% of patients reached this milestone ( $p < 0.001$ ).<sup>81</sup> This benefit was durable out to 96 weeks.<sup>82</sup>

Following on from this, the STARTMRK study was conducted—a randomized double-blind trial in antiretroviral naive patients comparing raltegravir against efavirenz, with a nucleoside backbone of tenofovir-emtricitabine. At 96 weeks, raltegravir was found to be non-inferior to efavirenz in regard to virological suppression (81% patients on raltegravir and 79%

on efavirenz achieved a viral load of less than 50 copies/mL;  $p < 0.001$ ).<sup>83</sup> The raltegravir arm had a faster rate of virological suppression and was associated with a greater CD4 count increase compared with the efavirenz arm at 48 weeks of treatment,<sup>84</sup> but there was no significant difference between arms at 96 weeks.<sup>83</sup> Despite this faster rate of virological suppression, the incidence of immune reconstitution syndrome was similar in both groups. The clinical benefit or harm of achieving immune restoration sooner has not been demonstrated yet.

The main clinical benefit of raltegravir lies in its tolerability. Patients randomized to raltegravir in STARTMRK experienced significantly less adverse effects compared to efavirenz (47% vs. 78%;  $p < 0.001$ ), although discontinuation rates were not dissimilar (4% vs. 6%;  $p = 0.333$ ).<sup>83</sup> One concern raised in the studies listed above was the rate of newly diagnosed, recurrent or progressive malignancies—3.5% of raltegravir-treated patients in BENCHMRK, compared with 1.7% of those receiving placebo—this equated to a relative risk of cancer of 1.54 (95% CI, 0.50–6.34)<sup>81</sup>—the implications of which remain unknown as carcinogenicity was not seen in preclinical studies. Drug interactions may also occur, but unlike many other antiretrovirals that are metabolized by the cytochrome P450 system, raltegravir is affected by changes in the enzyme uridine diphosphate glucuronosyltransferase 1A1.<sup>85</sup>

## What to Start?

After the decision is made to commence treatment, the selection of the first ART regimen is important given the clear evidence for lifelong therapy.<sup>4</sup> With this in mind several factors play a role in deciding the choice of agents used. First and foremost is obviously virological efficacy and robustness, but other considerations include pill burden, toxicity, co-morbidities and drug interactions, and finally patient preference.<sup>44,67</sup>

Most recommendations suggest the use of two NRTIs in combination with a third agent from a different class with current evidence suggesting the use of an NNRTI, PI or INSTI.<sup>44,67</sup> In the past there was some consideration given to triple or even quadruple NRTI regimens but these have been clearly shown to be inferior in virological response<sup>86–88</sup> and with the advent of some newer classes of ART, such as the integrase inhibitors or CCR5 co-receptor antagonists, the need to reserve drugs in case of future resistance is less of an issue.

The preferred NRTI backbone currently is tenofovir–emtricitabine (TDF–FTC) primarily due to its once daily dosing and low side effect profile. In studies comparing its efficacy against zidovudine–lamivudine (AZT–3TC), TDF–FTC was superior in terms of virological suppression at 144 weeks (71% vs. 58%;  $p = 0.004$ ), less discontinuation due to side effects (5% vs. 11%;  $p = 0.01$ ), less lipodystrophy ( $p < 0.001$ ) and fewer patients developed the M184V mutation ( $p = 0.02$ ).<sup>89</sup>

Up until recently the fixed-dose combination (FDC) of abacavir and lamivudine was one of the preferred components of the initial ART regimen. It is now recommended as an alternative,

rather than a first-line option for a number of reasons. ACTG A5202 demonstrated more virological failures in antiretroviral naive patients treated with abacavir–lamivudine as compared to those treated with tenofovir–emtricitabine in those with high viral loads ( $>100,000$  copies/mL)<sup>90</sup> although this effect was not confirmed in the subsequent HEAT trial.<sup>91</sup> Also more recently, the observation of greater cardiovascular risk in patients currently on abacavir or having received it within the past 6 months<sup>92</sup> has resulted in a reduction in its use—although the biological mechanism for the increased cardiovascular risk is yet to be determined.<sup>93</sup> In its favor is its high central nervous system (CNS) penetrance,<sup>94,95</sup> which may be of benefit in those with neurocognitive diseases and it also has once daily dosing. No patient should start ABC or a combination containing ABC until they are confirmed to be HLA-B5701 negative to avoid potentially fatal hypersensitivity reactions.<sup>66</sup>

The FDC of zidovudine–lamivudine (AZT–3TC) is also an option for the NRTI backbone but is generally not considered a preferred first-line combination. AZT–3TC requires twice a day dosing and has more side effects experienced in general when compared with TDF–FTC<sup>89</sup> or ABC–3TC<sup>96</sup>. However, there is considerable clinical experience with its use and the safety profile is well-known. It remains a preferred agent in the setting of pregnancy.

In combination with an NRTI backbone, there are several options for the third first-line agent used. Current evidence supports the use of either an NNRTI, PI, or INI.

Efavirenz remains the preferred NNRTI of choice. In naive studies efavirenz has been demonstrated to achieve sustained virologic suppression for more than 5 years. In comparison with PIs, efavirenz has been shown to be superior to indinavir and lopinavir–ritonavir, and also comparable to atazanavir.<sup>44,97,98</sup> Of concern is the low genetic barrier to resistance within the NNRTI class in general. For this reason, baseline genotypic analysis is important to exclude pre-existing transmitted NNRTI resistance which is estimated to occur in between 2.3% and 9.1% of ART naive patients.<sup>99–101</sup> The CD4 cell count constraints on the use of nevirapine (see above)<sup>69</sup> limits its use in the ART naive setting except for late presenting patients with low CD4 cell counts. The introduction of the FDC of tenofovir, emtricitabine, and efavirenz further reduces pill burden to a single pill, once daily which potentially assists with compliance of treatment that will need to be lifelong.

Within the PI class, atazanavir and darunavir are the preferred agents for first-line use. Atazanavir is a once daily PI that was first shown to be non-inferior to efavirenz in treatment of ART naive patients in combination with a zidovudine–lamivudine NRTI backbone.<sup>97</sup> By week 48, 70% of patients treated with atazanavir had a viral load of less than 400 copies/mL, as compared with 64% of patients receiving efavirenz. Increases in CD4 counts were similar between the treatment arms and atazanavir was well-tolerated in terms of lipid profile. Hyperbilirubinemia only rarely led to drug discontinuation ( $<1\%$ ).

The CASTLE study was a randomized, open label study comparing ritonavir-boosted lopinavir twice daily with boosted atazanavir once daily.<sup>102</sup> In total 883 patients were enrolled over



96 weeks. By the end of the study, the atazanavir arm achieved non-inferiority in virological suppression (74% vs. 68%;  $p < 0.05$ ). More patients complained of gastrointestinal side effects in the lopinavir arm, although conversely there were more instances of hyperbilirubinemia in the atazanavir arm. Rates of suppression were similar regardless of HIV RNA cut-off or baseline CD4 count.

In the ARTEMIS trial, 689 ART naive patients were randomized to ritonavir-boosted darunavir (800 mg) or ritonavir-boosted lopinavir. At 48 weeks, darunavir was shown to be non-inferior to lopinavir with regards to virological suppression (84% vs. 78%;  $p < 0.001$ ).<sup>103</sup> By 96 weeks of follow-up darunavir was superior in virological suppression after intent-to-treat analysis (79% vs. 71%;  $p = 0.012$ ) and this difference was mainly seen in those with a CD4 count less than 200 at baseline (79% vs. 65%;  $p = 0.009$ ) and those with a high baseline viral load ( $\geq 100,000$  copies/mL) (76% vs. 63%;  $p = 0.023$ ).<sup>104</sup> Sub-optimal adherence to darunavir, compared with lopinavir, had less of an effect on rates of virological suppression (76% vs. 53%;  $p < 0.01$ ).<sup>105</sup>

When choosing between PIs and NNRTIs, there may be several factors to consider. Efficacy is generally not a major discriminating factor but rather tolerability. The single pill formulation of TDF-FTC-EFV is a significant incentive for patients concerned about pill burden or with compliance issues. This regimen is generally well-tolerated although a small percentage will develop rash, necessitating discontinuation, and the CNS side effects of efavirenz can be disconcerting for some patients, or dissuade against use in others with pre-existing psychiatric disease. PI-based regimens are less lipid friendly and are generally associated with more GIT disturbance due to the concomitant use of ritonavir.<sup>44</sup>

More recently, the integrase inhibitor, raltegravir (RAL) was shown in the STARTMRK trial to be non-inferior with regard to viral suppression to efavirenz (81% vs. 79%;  $p < 0.001$ ) when used in combination with TDF-FTC,<sup>83</sup> although no comparison has been made yet with PI-based regimens. In comparison to efavirenz, patients treated with raltegravir experienced fewer side effects in general (47% vs. 78%;  $p < 0.001$ ) although serious adverse events and toxicity requiring discontinuation of treatment was similar between groups. Raltegravir also had a better lipid profile compared with efavirenz. This data prompted its inclusion as a preferred first-line agent although some have concerns about its use as a first-line agent when it has significant benefits currently for the treatment of multi-class experienced patients.<sup>82,106</sup> Similar to NNRTIs, it too has a low genetic barrier to resistance.<sup>107</sup>

The above regimens are only recommendations and as mentioned already, there are numerous factors to consider when initiating patients on ART for the first time. With the number of agents available a large number of combinations are possible—there are a few combinations that are not recommended and these are listed in the DHHS guidelines.<sup>44</sup>

## SECOND-LINE OPTIONS

A change in ART regimen may be required either for viral resistance, drug intolerance, toxicity or due to potential drug interactions with concomitant medications.

Virological failure is defined as failure to fully suppress viremia ( $<50$  copies/mL at 24 weeks) or recrudescence after previous suppression, and it always warrants a change in ART regimen. Virological failure, even if at low levels of viremia, is associated with the development of resistance mutations<sup>108–111</sup> that will limit future therapeutic options as they accumulate. However, very low-level viremia ( $<1000$  copies/mL) may not necessarily warrant a change in ART regimen immediately, but rather careful observation.<sup>44</sup> Detectable viremia should be confirmed by a second test prior to considering a change in therapy. ART failure may sometimes be due to previously archived resistance not seen on the baseline genotype; transmitted resistance is becoming an increasing problem with the increasing availability of ART, rates of 9.1% were reported in a recent European surveillance report.<sup>99</sup> More commonly, viral resistance develops on ART due to inadequate compliance or drug interactions. It is important to address these issues prior to changing therapy.

Drug toxicity or poor tolerance is often easier to manage because with the number of ARVs available today, patients can often be switched to another drug within the class without the need for new resistance testing and with good effect. Substituting a single drug to one from a different class to manage drug toxicity may be reasonable in the setting of a fully suppressed viral load. However, it is important to have confidence that the remaining two (or more) antiretrovirals will have enough activity to maintain a barrier to development of resistance and to consider any potential drug interactions that would compromise efficacy.<sup>112</sup> Similarly, drug interactions are less of an issue today due to the number of antiretroviral options available for use.

Despite more than 25 years of clinical antiretroviral drug trials, there is very little evidence for second-line treatment following on from first regimen failure.<sup>113</sup> An important principle to adhere to is to never change a single drug in a virologically failing regimen—a minimum of two new fully active, and ideally three, antiretroviral drugs should always be introduced regardless of the HIV genotype which may not detect all mutations present. Results from the HIV genotype analysis, taken while the patient is taking the failing regimen (or within 4 weeks of ceasing it) guide the selection of the new antiretroviral regimen.<sup>112</sup>

Patients who fail on an NNRTI-containing regimen will often develop resistance to all the “first generation” NNRTIs and hence lose activity to the entire class except perhaps for etravirine, whose activity varies according to which NNRTI mutations have developed.<sup>114,115</sup> NRTI mutations frequently develop following NNRTI resistance to essentially lead to single ARV class therapy in this setting.<sup>112</sup> The DUET 1 and 2 studies showed that etravirine still has considerable efficacy (see above) in patients with known NNRTI and PI resistance, although all patients did receive ritonavir-boosted darunavir as well.<sup>70</sup>

On the other hand, failure on a protease inhibitor containing regimen does not necessarily infer the development of broad resistance mutations for PIs due to their inherent higher genetic barrier to resistance.<sup>99,116,117</sup> In fact, major PI resistance mutations

occur in less than 1% of patients failing their regimen for the first time.<sup>112</sup> If major PI mutations do occur, then a second generation drug such as ritonavir-boosted darunavir or tipranavir will likely still have efficacy as demonstrated by the RESIST and POWER studies.<sup>118–120</sup> One of the few trials to assess choice of ART at first virological failure was the TITAN study,<sup>121</sup> which compared the use of boosted lopinavir to boosted darunavir containing regimens in patients with virological failure. It showed that at 48 weeks, darunavir was superior to lopinavir in terms of viral suppression below 400 copies/ $\mu$ L but especially so in patients who had previously been treated with a PI-containing regimen.

A number of the more recently developed antiretrovirals have demonstrated benefits in the setting of heavily treatment-experienced patients. As mentioned earlier, maraviroc in MOTIVATE, raltegravir in BENCHMRK, enfuvirtide in TORO, etravirine in DUET, and darunavir in the POWER studies have all demonstrated clinical efficacy in the setting of multiple ARV class resistance. The final guide in choosing active drugs for a salvage regimen is the use of combined results of genotypes from throughout a patient's treatment history. However the combination of ritonavir-boosted darunavir, etravirine, and raltegravir has shown promise in the treatment of multi-drug-resistant HIV.<sup>106</sup>

Finally, it is possible to have discrepant HIV control within an individual patient, i.e., in different body compartments—the most obvious being the central nervous system (CNS). Owing to the variable penetration of ARVs into the CNS,<sup>94,95</sup> patients may have virological suppression in plasma but have replicating virus within the CNS. While this remains an uncommon occurrence, it may be important to consider the possibility in patients on cART who present with HIV-associated neurological and psychiatric disorders.<sup>122</sup>

## Treatment in Special Groups

### PREGNANCY

Pregnancy in HIV-positive women poses a number of unique considerations: firstly the effect of pregnancy on HIV progression in the mother; secondly the risk of HIV transmission to the child; thirdly the change in drug metabolism and pharmacokinetics in different stages of pregnancy, and lastly the risk of ART on the developing fetus.

Pregnancy appears not to have any major deleterious effects on HIV in the mother. Despite some initial concerns that HIV progressed more rapidly during pregnancy, there is no increase in mortality compared with uninfected mothers, no change in HIV viral load, and no increased risk of opportunistic infections or AIDS events.<sup>123</sup> CD4 cell counts do drop during pregnancy but CD4 percentages remain the same<sup>124</sup> reflecting a physiological change in lymphocyte numbers rather than a true fall in immunity.

### Antepartum Antiretroviral Therapy

Of more concern to mothers is the risk of vertical transmission to their child. In the absence of ART, mother to child transmission

(MTCT) occurs in approximately 25% of deliveries.<sup>125</sup> The majority of transmission occurs during labor and delivery, but approximately a third of transmission will occur during pregnancy, especially in the later stages of gestation. ART has been clearly documented to reduce the risk of MTCT. The first study of ART in pregnancy with zidovudine monotherapy (PACTG 076)<sup>125</sup> demonstrated a 68% reduction in transmission rate and although benefit of the same magnitude with single agent therapy has not been reproduced, a number of observational studies confirmed the benefit of monotherapy.<sup>9,126,127</sup> There have been no randomized studies of cART against placebo for obvious reasons but again observational studies suggest that transmission rates of less than 2% can be achieved.<sup>128,129</sup>

The maternal viral load at the time of delivery is a key determinant of transmission risk<sup>130</sup> and hence virological suppression during pregnancy managed with cART is now considered standard of care<sup>131</sup> in many countries. There are some who would still suggest that in women with low viral loads, zidovudine monotherapy may be sufficient, especially when combined with elective caesarean section.<sup>132,133</sup>

In favor of monotherapy, ART has been associated with an increased rate of preterm delivery<sup>134,135</sup> independent of maternal age. The European collaborative study found that the risk of prematurity was greater with cART than with monotherapy (OR 1.43; 95% CI 1.1–1.86;  $p=0.01$ )<sup>133,134</sup> and hence the additional benefit of cART over monotherapy in terms of MTCT should be weighed against the increased risk of preterm delivery.<sup>136</sup> Townsend et al. estimated that to prevent 100 vertical transmissions by using cART, as opposed to monotherapy, 63 additional preterm deliveries would result (95% CI 6–196) of which, 23 would occur before 32 weeks gestation. Other studies have not associated ART with increased rates of premature births and a meta-analysis suggested that overall there was no strong association although many different populations were studied, each with their own set of confounders.<sup>137</sup> When choosing between monotherapy and cART, it is important to decide on the primary aim of therapy—prevention of transmission to the infant where monotherapy may be enough in some circumstances, or control of maternal HIV disease with combination treatment, which is generally considered the standard of care.<sup>44,67</sup>

Different antiretroviral drugs vary in their safety record in pregnancy. Agents with the most safety data include zidovudine–lamivudine (AZT–3TC) fixed-dose combination (FDC) (Combivir), together with lopinavir–ritonavir (Kaletra) or nevirapine in those women with low CD4 cell counts.<sup>131</sup> Zidovudine (AZT) is generally recommended as part of cART in pregnant women as it has the greatest evidence and safety data to support it. This is not to say that non-AZT containing regimens cannot be used if there are reasons why AZT should not be used; for example, if compliance, side effects or resistance are an issue; or if the woman in question is already on a fully suppressive non-AZT containing regimen.<sup>131</sup>

There have been previous concerns regarding the use of efavirenz, primarily related to congenital central nervous system

abnormalities including neural tube defects (NTDs) that were seen in pre-clinical testing in primates. Given these concerns, efavirenz has been given a category D safety in pregnancy rating and recommendations are generally that pregnant women should be switched off it as soon as possible and perhaps not even commenced in women of child-bearing potential. Case reports and retrospective case series of birth defects have been published, as well as a recent meta-analysis which all suggest that there is no significant difference in the rate of congenital abnormalities seen in children born to mothers treated with efavirenz.<sup>138</sup> Obviously this data must be interpreted with a degree of caution as it is not truly randomized, prospective evidence, however, the initial concern regarding efavirenz may not be as great as once thought. The alternative NNRTI, nevirapine, has a good safety record if initiated in women with a CD4 count below 250 cells/ $\mu$ L, thereby avoiding the increased risk of hypersensitivity, rash, and hepatic toxicity associated with use at higher levels of immunity.<sup>69</sup>

Other reverse transcriptase inhibitors of concern in pregnancy include tenofovir, which despite its strong preference in first-line treatment of HIV, is used with caution antenatally due to animal reports of fetal osteopenia and bone demineralization in children.<sup>131</sup> Protease inhibitors (PIs) are generally well-tolerated with the most safety data belonging to the FDC of lopinavir-ritonavir. Atazanavir and indinavir pose theoretical concerns of neonatal jaundice and kernicterus, although this has not been borne out in clinical studies.<sup>131</sup> Drug levels of PIs may be reduced in pregnancy and as such ritonavir boosting is generally recommended.

Other than the teratogenic potential of ART it is also important to remember the major physiological changes in pregnancy that affect pharmacokinetics and pharmacodynamics of these medications which may alter dosing recommendations.

### Antiretroviral Therapy during Labor

In addition to antepartum AZT monotherapy, the PACTG 076 study also treated women with intravenous AZT during labor.<sup>125</sup> An infusion commenced 3 hours prior to elective caesarean section, and continued for an hour post delivery has become standard practice, regardless of whether the mother received cART during her pregnancy or not.<sup>131</sup> AZT confers benefit to both the mother and the newborn as it crosses the placenta, and is likely to still be useful in the setting of apparent AZT resistance in the mother.<sup>139</sup>

### Caesarean Section

Elective caesarean section is another method utilized to reduce the risk of vertical transmission. During vaginal delivery a newly born infant is exposed to maternal blood and fluids in the birth canal and hence delivery by caesarean section, if performed prior to the rupture of membranes, eliminates this risk. Adjusting for AZT monotherapy, caesarean section was shown to reduce the risk of vertical transmission by 57% (OR 0.43, 95% CI 0.33–0.56).<sup>140</sup> Together with AZT treatment, the risk of transmission following

delivery is reduced significantly (OR 0.07, 95% CI 0.09–0.19). This magnitude of benefit becomes less clear once cART is used given the greater viral suppression that is achieved. In one prospective study of caesarean section, no significant benefit on vertical transmission was seen once cART was accounted for (OR 0.52, 95% CI 0.14–2.03;  $p = 0.36$ ) (MTCT in HIV, CID 2005). Hence, the reduction in risk of transmission of HIV but the increased risk associated with caesarean section may not be acceptable to a patient virologically suppressed on cART and these risks need to be discussed with women during their antenatal care.<sup>131</sup>

### Post-Partum Antiretroviral Therapy

Following delivery, the decision to continue ART should be made after consultation with the mother and taking into account her immune status and co-morbidities. It may be that she would fulfil general criteria requiring treatment in non-pregnant adults and as such it would be advisable to continue ART. If not, it is not unreasonable to cease ART. Mothers treated with an NNRTI as part of their cART antenatally need to be aware of the prolonged half lives of NNRTIs that may require either a staggered discontinuation (i.e., NNRTI first, then NRTIs a minimum of 1 week later) or perhaps substitution of the NNRTI with a PI for a month before ceasing all drugs. These steps reduce the risk of developing NNRTI resistance upon cessation of ART.<sup>131</sup>

### Breast Feeding

Breast feeding for infants in industrialized and middle-income countries is not recommended due to the clearly documented risk of HIV transmission via breast milk.<sup>141</sup> This can occur despite adequate maternal ART as concentrations of ART within breast milk can be erratic—either high leading to potential infant toxicity; or low—promoting development of viral resistance. This recommendation differs from the recommendations on breast feeding in resource limited settings where the positive benefits of breast feeding on childhood morbidity and mortality far outweigh the risks of HIV transmission.<sup>142</sup>

### Newborn Care

Given maternal antibodies can persist in the newborn for 12–18 months, HIV infection of the infant is made by the presence of HIV DNA in blood on two different occasions, 1 month after delivery. Until infection is confirmed or excluded, the newborn should receive prophylaxis with zidovudine (2 mg/kg, four times daily if born at term) for 6 weeks.<sup>125,131</sup>

### Co-Infection With HEPATITIS B/C

HIV has been clearly demonstrated to result in a faster clinical course of viral related liver disease in both hepatitis B (HBV) and hepatitis C (HCV)<sup>143,144</sup> and consequently, treatment of HIV in patients with co-infection should be of benefit.



A number of the anti-HIV medications are active against HBV as well (and are available as monotherapy for treatment of HBV monoinfection), e.g., lamivudine, emtricitabine, and tenofovir. To avoid the development of HIV resistance to single antiretroviral use, the decision to treat HBV often necessitates initiation of treatment of HIV with cART—most often using the FDC of tenofovir and emtricitabine, Truvada, together with a third agent from a different class. Caution must be taken in ceasing ART in a patient with chronic HBV as the consequent reduction in immunity and flare in HBV replication can lead to a clinical flare of hepatitis.<sup>145</sup>

For dual infection with HIV and HCV there is no issue with overlapping activity of antiviral medications used and hence it is possible to treat either disease independent of each other. However, by improving the immune response with cART, improved responses in HCV treatment with pegylated interferon and ribavirin are seen.<sup>146</sup> Given the significant commitment involved for patients to undergo a 6 or 12 month course of HCV therapy with its associated side effect profile, it would seem prudent to treat the HIV first, if possible, to ensure the best chance of a sustained virological response (SVR), especially in the cases of genotypes 1 and 4 infection. For patients with higher CD4 cell counts not necessitating ART on their own merit, treatment of HCV infection first may avoid potential overlapping drug toxicity and interactions.<sup>67</sup>

Obviously, there is some concern of increased rates of liver toxicity with cART in patients with pre-existing liver disease, but generally this is not clinically relevant except for the case of potentially fatal nevirapine hypersensitivity reaction when patients are started at high CD4 cell counts.<sup>69</sup> In fact treating the underlying liver disease, e.g., clearing HCV infection can reduce the rates of hepatotoxicity seen with ART.<sup>147</sup>

## PRIMARY HIV INFECTION

In general, treatment of primary infection is not recommended especially if the patient is asymptomatic.<sup>67</sup> When symptomatic, the acute seroconversion illness is generally self-limiting and so the benefit of early ART remains largely theoretical—preservation of immune function, reduction in disease progression, reduction in viral reservoirs and decrease in the risk of HIV transmission.<sup>44,148</sup> However, this approach would essentially commit the individual to lifelong therapy. Given the potential risks and benefits of this approach remain unproven, treatment of primary infection is generally not recommended.

## ADOLESCENTS

Adolescents are often grouped with adults in reports and studies in HIV, but adolescents infected with HIV pose a unique set of issues and care needs due to a variety of clinical, behavioral, developmental, and psychosocial changes that occur at this developmental stage. Concerns over disclosure, adherence, and sexual identity are just some of the issues that face children entering adulthood that is complicated by the natural shift in

responsibility to themselves for the management of a chronic, and currently incurable, disease.

Adolescents with HIV can be divided into two broad groups—those with perinatally acquired infection and those who have acquired infection through high-risk behavior, either sexually or via injecting drug use.<sup>149</sup>

Those with perinatally acquired infection are likely to have already been exposed to medical care for most of their life, already be on ART, and frequently have drug resistance<sup>150</sup>—all before beginning normal adolescent risk taking behavior and psychosocial development. These adolescents may already have complications because of their HIV status, such as delayed puberty, or from their ART, such as lipodystrophy. Behaviorally acquired HIV-infected adolescents on the other hand are likely to have only been infected recently and may still be coping with the diagnosis—depression and low self-esteem are common. ART initiation may not be an immediate concern but rather disclosure to family and friends, as well as the acceptance of a chronic illness and the incumbent responsibilities that will place on themselves in terms of medical care and ART.<sup>149</sup>

The transition from childhood to adulthood is also accompanied by physiological changes that affect the dosing of ART but very little data exists on the pharmacokinetics and pharmacodynamics of antiretrovirals in adolescence.<sup>151</sup> Some groups advocate dosing adolescents over the age of 12 years old as adults.<sup>152</sup> The US guidelines suggest ART should be dosed according to the Tanner staging of puberty—stage 1 and 2 dosed as children and stage 3 and 4 as adults.<sup>44</sup> There is actually very little clinical data supporting this recommendation but certainly there is evidence of changes in cytochrome P450 metabolism during puberty which could justify using Tanner stage rather than simply being guided by weight or age. Even within these pubertal stages, the growth spurts of adolescence can make dosing unpredictable and patients need to be closely monitored for both effectiveness of ART as well as excess toxicity.<sup>149</sup> Within this context, therapeutic drug monitoring may also assist in selecting the correct doses for individuals.<sup>151</sup>

ART adherence, which is obviously paramount in achieving virological suppression, is often difficult among adolescents—one review of adherence interventional studies in adolescence found a baseline range of between 28.3% and 69.8% compliance.<sup>153</sup> Adherence is difficult to achieve in adolescents in general but within HIV-infected individuals, factors associated with non-compliance include fear of discrimination or accidental disclosure to family and friends, poorer education level and socioeconomic status, substance use, depression, and use of “escape” coping.<sup>153</sup> Mechanisms to improve compliance include parental involvement, informative discussion of side effects, support groups or even short-term hospitalization.<sup>149</sup>

## PEDIATRICS

Children infected with HIV face a more rapid progression of disease compared with infection acquired in adulthood.

**Table 114.4:** Indications for Treatment of HIV-Positive Children

Age	CD4/viral load threshold	Clinical
<12 months	Treat all children <12 months age	
1–5 years old	CD4 < 25% at any viral load	Treat if symptomatic
	CD4 ≥ 25% if viral load > 100,000 copies/mL	
≥ 5 years old	CD4 < 350 cells/mm <sup>3</sup> at any viral load	Treat if symptomatic
	CD4 ≥ 350 cells/mm <sup>3</sup> if viral load >100,000 copies/mL	

Adapted from the Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, 2010.<sup>155</sup>

Approximately, one quarter of babies with perinatally acquired infection progress to AIDS within a year, the remainder generally progress within 5 years.<sup>154</sup>

Most antiretroviral drugs available for use in adults can be used for the treatment of children<sup>44</sup> although there is obviously less safety data for this group. The main difference for children is the timing of treatment. All babies less than a year old with perinatally acquired infection should receive treatment owing to the rapid progression of untreated HIV in this population. After this first year of life, treatment is guided by CD4 cell counts at different ages (see Table 114.4). All children with CD4 cell counts within the moderate to severe immunosuppression range should receive treatment, as well those who are symptomatic regardless of CD4 cell count.<sup>155</sup>

## Monitoring

Once ART has been commenced in a patient there are a number of issues that need to be monitored by the treating clinician.

## Toxicity

In the short term, it is important to address any immediate toxicity caused by the new regimen. Minimizing and appropriate management of toxicities are important to patient's quality of life and clearly affect medication adherence.<sup>156</sup> Some adverse effects may just be transient and will resolve spontaneously with persistence with medication—this often includes some early gastrointestinal disturbance with the PIs and some scleral icterus with atazanavir. Many patients will continue their ART if reassured that most often these symptoms will improve. On the other hand, severe toxicity needs to be addressed promptly to avoid non-compliance and a loss of trust in the treating clinician.

## Adherence and ART Efficacy

After 1 month of ART it is routine to measure the patient's CD4 cell count and HIV viral load. At least one log fall in viral

load should be expected in patients compliant with their ART regimen effective against a susceptible virus.<sup>44</sup> If the viral load has not fallen by at least this amount it may signify either previously undetected resistance, or more often poor adherence. At least 95% adherence with all doses of medications had been shown to be necessary to achieve virological suppression in patients on cART during the era of unboosted protease inhibitors,<sup>157</sup> but the advent of ritonavir boosting as well as antiretrovirals with long half lives (e.g., efavirenz) has made this requirement more forgiving. The average adherence to boosted PIs appears to be related to efficacy, whereas consecutive missed doses of NNRTIs appear to promote resistance.<sup>158,159</sup> Regardless of the ART regimen, clarifying adherence is important—either by self reporting, pill counting, and therapeutic drug level monitoring for some agents. If adherence appears to be adequate, viral resistance testing is warranted in case the first ART regimen used has unmasked previously undetected viral resistance.

In the longer term, CD4 cell counts and HIV viral loads are generally monitored every 3–4 months—used as a measure of the host immune system. The goal of ART, as mentioned previously, is virological suppression below the level of detection by current assays.<sup>44</sup> Ideally the CD4 cell count should increase significantly also but there are a number of factors involved in its recovery that are independent of the efficacy of ART including nadir CD4 cell count, previous therapeutic failure, HCV co-infection, age, and adherence.<sup>160–163</sup> Viral resistance testing should be performed while the patient is still on ART or at most ceased less than 2–4 weeks prior, if there is consistent evidence of virological failure during ART.<sup>44</sup>

## Immune Reconstitution

Individuals may in fact develop immune responses to organisms previously unrecognized by the host immune system owing to the degree of immunosuppression they experienced prior to commencing ART. The rapid fall in HIV viral load and corresponding increase in CD4 cell count which the patients experience with the initiation of ART has been shown to correlate with the risk of this immune reconstitution inflammatory syndrome (IRIS). Other identified risk factors include a low baseline CD4 count, previously ART naive patients, and those initiated on ART near to the time of diagnosis of an opportunistic infection.<sup>50</sup> Retrospective studies previously suggested quite high rates of IRIS in up to a third of patients commencing ART,<sup>50,164,165</sup> but one prospective study described IRIS occurring in 10.4% of patients.<sup>166</sup>

## Non-AIDS Events

With the advances in ART achieved in the past 20 years, the incidence of opportunistic disease and AIDS related events has fallen dramatically. While the overall mortality rate has fallen, residual viral replication below the limits of detection, with subsequent chronic immune activation and inflammation has led to an increased risk of “non-AIDS” events. HIV-positive patients

experience an increased rate of cardiovascular, renal, hepatic, neurological and bone disease; as well as a higher incidence of non-AIDS-related malignancies.<sup>167–170</sup>

### Summary

In absence of cure, the aim of HIV treatment is the suppression of viremia, which has been shown to lead to immune recovery, increased CD4 cell count, reduced mortality, and reductions in both AIDS related and “non-AIDS” related events.

Combination HIV treatment should certainly commence below a CD4 count of 350 cells/mm<sup>3</sup> with good randomized controlled data to support this. Between 350 and 500 cells/mm<sup>3</sup>, treatment should be considered on an individual patient basis, especially in the setting of hepatitis co-infection, high cardiovascular risk, malignancy, high viral load, rapid CD4 cell count decline, or pregnancy. Above a CD4 cell count of 500 cells/mm<sup>3</sup> some experts would consider combination antiretroviral therapy (cART) on the basis of observational data and hypothesized benefits, but there is little clinical data to support this recommendation currently.

In the setting of acute opportunistic infection (OI), the optimal timing of initiation of cART appears to vary somewhat based on the infective organism but in general terms should begin early, during the treatment of OI, but with enough time to allow some recovery from the specific OI.

In pregnant women, suppression of maternal viremia by the time of delivery is essential to reduce the risk of mother-to-child transmission. Other interventions that reduce this risk include elective caesarean section, intravenous zidovudine during labor, avoidance of breast feeding, and treatment of the newborn with zidovudine for 6 weeks post delivery.

As of 2010, at least 15 drugs from 6 different drug classes are available for commercial use. Combination antiretroviral therapy should include a minimum three drugs from at least two different drug classes aiming to provide the best tolerated, most durable, and least toxic regimen possible.

Once initiated, it is essential to continue monitoring patients regularly for potential drug toxicity, adherence and cART efficacy, immune reconstitution events and also non-AIDS events.

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# Guidelines for the Treatment of HIV and AIDS in Resource-Limited Countries

Chris Duncombe • Deepti Suri

# 115

## Introduction

The World Health Organization (WHO) has been promoting a public-health approach for antiretroviral therapy (ART) to improve access in resource-poor settings. The public-health approaches for ART have been developed to support decentralized implementation in resource-poor countries. However, these guidelines have to be adapted according to local healthcare system.

In 2003, UNAIDS and WHO launched a global strategy, “3 by 5” initiative, to provide ART to three million people living with HIV/AIDS in 50 developing countries. This program was subsequently replaced by The Global Fund for AIDS, Tuberculosis, and Malaria as well as bilateral support like the President’s Emergency Plan for AIDS Relief (PEPFAR).

By the end of 2007, over 10 billion dollars had been donated and disbursed for the HIV pandemic in developing countries. WHO estimated that the number of people in low and middle-income countries who were receiving ART on July 2009 to be 4 million; however, an estimated 7 million eligible HIV-infected people were still in need of treatment.<sup>1</sup>

The development of generic medications has been an important advance in making ART available in resource-poor countries.<sup>2</sup> In Zambia, for example, 21,755 adults were enrolled into HIV treatment programs at 18 primary care facilities over 19 months.<sup>3</sup> In India, the National Aids Control Organization (NACO) is responsible for coordinating the overall response to HIV/AIDS, including that of the health sector, supported by the state AIDS control societies at the state level. The National AIDS Control Programme was launched in 1987, with the objective to reduce the transmission of HIV through a decentralized and comprehensive programme for generating awareness, changing behavior, targeting vulnerable groups, and conducting research. On November 30, 2003, the government announced a policy and programmed commitment to provide ART free of charge, with implementation starting on April 1, 2004. The availability of generic fixed drug combination regimen has revolutionized the management of these patients.

The guidelines given by WHO are the source documents used in the preparation of this chapter.

- *Antiretroviral Therapy for HIV Infection in Adults and Adolescents in Resource-Limited Settings: Towards Universal Access: Recommendations for a Public Health Approach (2006 revision)*. World Health Organization (Geneva).
- *Management of HIV infection and antiretroviral therapy in adults and adolescents: A clinical Manual*, 2007 World Health Organization, Regional Office for South-East Asia, Delhi.
- *Antiretrovirals for HIV: A Compilation of Facts and Product Information 2006*. World Health Organization, Regional Office for South-East Asia, Delhi.
- *Management of HIV Infection and Antiretroviral Therapy in Infants and Children. A Clinical Manual*, 2006. World Health Organization, Regional Office for South-East Asia, Delhi.

Management of HIV infection not only caters to the adults but also extends to children and pregnant women. In any developing country, health policies in relation to HIV need to have a holistic approach for its success. Issues in pediatric diagnosis and treatment, management of pregnant females, and drug resistance to antiretrovirals are dealt in this chapter.

Many HIV-infected people are unaware that they are infected with the virus. The key factor in success of management of HIV infection is early identification of HIV-infected individuals by screening which in turn would result in early access to life-saving treatment and help prevent the spread of the infection.

## HIV Testing

HIV voluntary counseling and testing (VCT) may utilize a **patient-initiated or provider-initiated approach**. Patient-initiated VCT is the process whereby a patient, who wants to know his/her HIV status, requests a HIV test. VCT should be part of routine care at health facilities that provide antenatal services, diagnosis, and treatment for tuberculosis and sexually

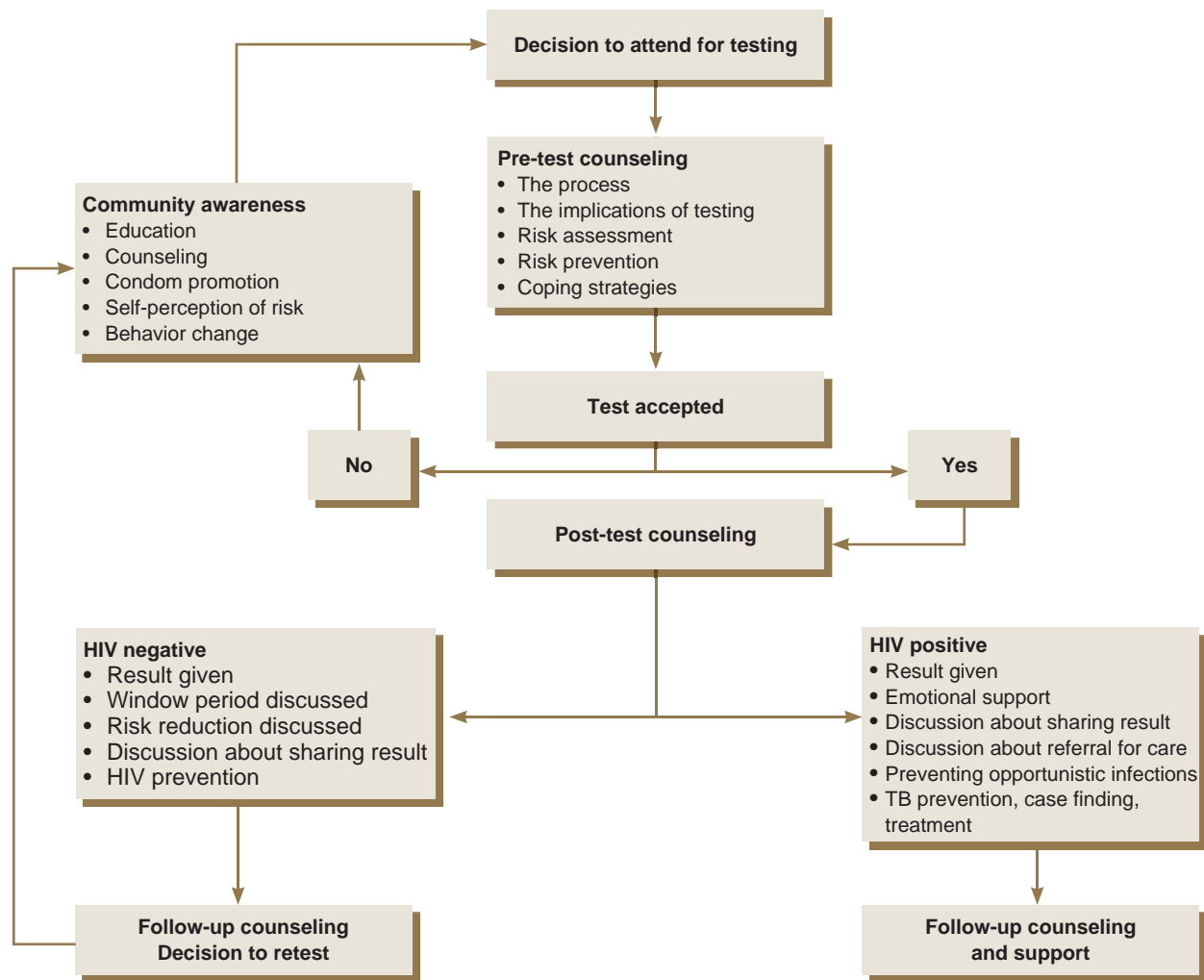


Fig. 115.1: HIV voluntary counseling and testing algorithm for adults and adolescents.

transmitted infections (Fig. 115.1). Provider-initiated HIV testing and counseling (PITC) is initiated by healthcare providers as part of all routine medical services. PITC has two main objectives; to confirm the HIV status of patients with suspected HIV-related symptoms, enabling medical services to be offered that would not be possible without knowledge of the HIV status of the person and to identify unrecognized HIV infection.

In an “opt-out” approach, patients may decline the HIV test if they do not want it to be performed. This approach may be suitable in situations where disclosure and discrimination may cause harm to the patient. An “opt-in” approach, where patients give consent to be tested rather than refusing a test, may be appropriate for vulnerable populations in some settings.

In an HIV-positive patient, the clinical signs and symptoms of HIV infection can be staged according to the established criteria. The WHO has given clinical and immunological staging of disease which could guide the physician in managing the patients (Annexure 1). Initiation of ART is guided according to the clinical as well as immunological staging.

## Initiating ART

### WHEN TO START ART IN ADULTS AND ADOLESCENTS

In resource-limited settings, ART is initiated based on clinical signs and symptoms, which are used to stage the severity of HIV disease using the WHO staging system. CD4 count is recommended prior to initiation of ART but its unavailability should not delay commencement of therapy. The precise time to start ART based on CD4 count is unknown but therapy should be started before CD4 count drops below 200 cells/ $\mu$ L. Pregnant women or patients with pulmonary tuberculosis with a CD4 count less than 350 cells/ $\mu$ L should also commence ART (Table 115.1).

### ASSESSMENT OF PATIENTS' READINESS FOR THERAPY

Managing patients on ART is complex due to the need for high rates of adherence to avoid the onset of drug resistance. This challenge is even more daunting in resource-poor nations where clinics are often understaffed and poorly funded.



**Table 115.1:** WHO's Clinical and Immunological Staging

Starting ART by clinical staging	
WHO Clinical Stage	Recommendation
1	Do not treat
2	Do not treat
3	<b>Treat</b>
4	<b>Treat</b>
Starting ART by CD4 count	
WHO Clinical Staging	CD4 testing available
1	Treat if CD4 cell count less than 200 cells/ $\mu$ L
2	
3	
	<ul style="list-style-type: none"> <li>Start ART before CD4 cell count drops below 200 cells/<math>\mu</math>L</li> <li>Start ART in pregnant women with WHO stage 3 or CD4 less than 350</li> <li>Start ART in patients with CD4 less than 350 and pulmonary TB (WHO stage 3) or severe bacterial disease</li> </ul>
4	Treat irrespective of CD4 count (Note: extrapulmonary TB is WHO stage 4)

However, it is imperative to inform the patient the need of lifelong ART.

- Build confidence and assess knowledge
- Explain ART and the objectives of the treatment
  - to avoid occurrence of OIs
  - to restore immunity
- Ensure the patient has understood
  - The treatment does not eliminate the virus
  - The treatment only suppresses the viral load
  - The treatment has to be taken regularly to avoid resistance
  - It is a lifelong treatment
- Advise and encourage the patient to disclose his diagnosis to his/her partner or family and support testing of the partner if status is unknown.

## ADHERENCE

The most common reason for ART failure is poor adherence.

- Treatment adherence should be strict and adherence to recommended regimens should be greater than 95% to avoid resistance.<sup>4</sup> This means that missing more than **3 doses per month** is associated with increased risk of drug resistance and failure
- Timing of drug intake is critical (drugs taken twice daily must be taken every 12 hours+/- one hour)
- Assessing readiness and commitment of patients for ART. Readiness to commence ART may be assessed by:
  - past ability to attend regular clinic visits and not miss appointments
  - past ability to take OI prophylaxis, such as cotrimoxazole
  - past ability to complete full course of TB therapy
  - adequate understanding

- If regular doses are missed or late, reinforce adherence counseling. Enlist community outreach teams and PLHA peer support groups as appropriate
- Treatment has to be continued for life
- Missed doses can be taken up to 6 hours in a BID regimen. If more than 6 hours late, skip dose and take next normal dose
- Drug side effects have to be understood and explained to the patient in advance of commencing ART
- People on ART need to continue to use condoms regularly and practice safe injecting use.

## RECOMMENDED AND ALTERNATIVE

### FIRST-LINE ANTIRETROVIRAL REGIMENS

Antiretroviral treatment regimens (Table 115.2) should have at least three active antiretroviral medications. Regimens are commonly discussed as having a “backbone” and a “base”. The backbone typically consists of two NRTIs. The base is either an NNRTI, or a PI. The available drugs and the formulations are compiled in Annexure 2.

## Antiretroviral Drug Toxicities

Side effects with ART are common; however, many side effects improve over time with continued administration. It is critically important for the clinician to differentiate between mild versus potentially serious adverse events when making decisions about continuing therapy. Some drug reactions are progressive with continued exposure and can be potentially life threatening. The patient must be counseled regarding these potentially serious adverse events and be told to stop therapy until the provider can evaluate them. However, frequent stoppage of drugs with prolonged “unstructured treatment interruptions” may promote resistance.

Details of the side effects and commonly implicated drugs and symptom directed toxicity management are summarized below in Tables 115.3 and 115.4.

## Cotrimoxazole Prophylaxis

Cotrimoxazole prophylaxis may be initiated in two different contexts.<sup>5</sup> “Classic” prophylaxis, where the target is the prevention of PCP and toxoplasmosis, is recommended for all HIV-infected adults with WHO stage 2, 3, and 4 HIV disease or with a CD4 count less than 200 cells/ $\mu$ L (if available). If the targets of prophylaxis are the reduction in morbidity and mortality associated with bacterial infections and malaria, in addition to the prevention of PCP and toxoplasmosis, cotrimoxazole is recommended for HIV

**Table 115.2:** WHO Recommended First-line and Alternative Antiretroviral Regimens

Regimen	Comments
<b>Preferred First-line regimens</b>	
<b>Zidovudine</b> + lamivudine + nevirapine or efavirenz	AZT may cause anemia and WHO recommends Hb monitoring. EFV is substituted for NVP intolerance and if patients are receiving rifampicin. Both NVP and EFV should be used with caution and careful monitoring in patients with known or suspected hepatic dysfunction. NVP should not be used in women with CD4 greater than 250 If EFV is not available, option in patients receiving rifampicin are NVP or a tripled nucleoside regimen (AZT + 3TC + abacavir) EFV may be used in women if they use consistent and reliable contraception EFV cannot be used in the first trimester of pregnancy but may be considered in the second and third trimester of pregnancy
<b>Tenofovir</b> + lamivudine + (nevirapine or efavirenz)	Calculation of creatinine clearance is recommended before initiating TDF and during TDF therapy. TDF is unavailable or expensive in many countries but this may change FTC is unavailable in many countries but this may change FTC/TDF co-formulation is available
<b>Alternative first-line regimens</b>	
<b>d4T</b> + lamivudine + nevirapine or efavirenz	d4T has significant toxicities (lipoatrophy, lactic acidosis, peripheral neuropathy) and careful clinical patient monitoring is recommended. WHO recommends that d4T should be phased out of treatment programs. d4T may continue to be used by many programs due to its availability and no requirements for laboratory monitoring.
<b>Abacavir</b> + lamivudine + nevirapine or efavirenz	Abacavir can cause a hypersensitivity reaction in some patients. This presents as constitutional signs and symptoms (including fever and rash) and abacavir should be stopped immediately and supportive therapy given. Rechallenge with abacavir following a hypersensitivity reaction can be fatal and should never be done. Abacavir is not commonly used in resource limited settings. It is expensive in most countries, although some generic versions are available

## Notes:

Emtricitabine (FTC) can be substituted for 3TC in any first-line regimen.

Lamivudine may be given as 300 mg OD. With tenofovir and efavirenz OD, this makes a convenient once/day regimen. AZT and nevirapine need to be dosed twice per day. Zidovudine 250 mg BID and 300 mg BID are both approved by WHO. Choice will depend on local availability.

**Table 115.3:** Antiretroviral Drug Toxicities

Time	Side effects and toxicities	Common drugs
Short term (the first few weeks)	Gastrointestinal toxicities nausea and vomiting, diarrhea	AZT, TDF, PIs
	Rash Most rashes occur within the first 2–3 weeks	NVP, EFV Abacavir PIs (rarely)
	Hepatotoxicity More common in hepatitis B or C co-infection	NVP, EFV PIs
	Drowsiness, dizziness, confusion, and vivid dreams Normally self-resolving but can take weeks to months	EFV
Medium term (the first few months)	Anemia and neutropenia	AZT
	Hyperpigmentation of skin, nails	AZT
	Lactic acidosis can occur at any time More common after the first few months Most commonly associated with d4T	d4T*, ddl, AZT
	Peripheral neuropathy can occur at any time More common after the first few months	d4T*,ddl
	Pancreatitis can occur at any time	ddl
Long term (after 6–18 months)	Lipodystrophy and lipoatrophy	d4T*, ddl, AZT, PIs
	Dyslipidemia	d4T*, EFV, PIs
	Diabetes	Indinavir
	Skin hair and nail abnormalities	PIs, especially Indinavir

\* Phasing out of d4T recommended by WHO.

Didanosine (ddl) and Protease inhibitors (PIs) are mostly used in second-line ART.

**Table 115.4:** Symptom Directed toxicity Management Recommendations

Toxicity	Causative ARVs	Recommendations
Acute pancreatitis	d4T* and ddI	Discontinue ART. Supportive treatment and laboratory monitoring. Resume ART with an NRTI with low pancreatic toxicity risk. (AZT, ABC, TDF)
Diarrhea	ddI (buffered formulation), LPV/r SQV/r	Usually self-limited, without need to discontinue ART. Symptomatic treatment should be offered.
Drug eruptions (mild to severe, including Stevens-Johnson syndrome or toxic epidermal necrolysis)	NVP, EFV (rarely)	In mild cases, antihistamines. Moderate rash, non-progressing and without mucosal involvement or systemic signs, consider a single NNRTI substitution (i.e., from NVP to EFV). In moderate and severe cases, discontinue ART and give supportive treatment. After resolution, resume ART with 3 NRTI or 2 NRTI + PI regimens.
Dyslipidemia, insulin resistance and hyperglycemia	PIs EFV	Consider replacing the suspected PI by drugs with less risk of metabolic toxicity
GI intolerance	All ARVs	Usually self-limited, without need to discontinue ART. Symptomatic treatment should be offered.
Hematological toxicities (particularly anemia and leukopenia)	AZT	If severe (Hb <6.5 g% and/or Absolute Neutrophil Count [ANC] <500 cells/ $\mu$ L) replace by an ARV with minimal or no bone marrow toxicity (e.g., d4T, ABC, or TDF) and consider blood transfusion.
Hepatitis	All ARVs (particularly with NVP and PI/r)	If ALT greater than 5-fold the basal level, discontinue ART and monitor. After resolution, replace the drug most likely associated.
Hyperbilirubinemia (indirect)	ATV	Generally asymptomatic, but can cause scleral icterus (without ALT elevations). Replace ATV for other PI.
Hypersensitivity reaction	ABC	Discontinue ABC and <b>do not restart</b> . Symptomatic treatment. Re-exposure may lead to a severe and potentially life-threatening reaction.
Lactic acidosis	All NRTIs (particularly d4T* and ddI)	Discontinue ART and give supportive treatment. After clinical resolution, resume ART, replacing the offending NRTI. ABC, TDF and 3TC are less likely to cause this type of toxicity.
Lipoatrophy and lipodystrophy	All NRTIs (particularly d4T*)	Early replacement of the suspected ARV drug (e.g., d4T* for TDF or ABC). Consider aesthetic treatment and physical exercises.
Neuropsychiatric changes	EFV	Usually self-limited, without need to discontinue ART.
Renal toxicity (nephrolithiasis)	IDV	If using IDV, interrupt IDV and offer hydration, laboratory monitoring and symptomatic treatment (50% recurrence rate). Consider replacing IDV for another PI.
Renal toxicity (renal tubular dysfunction)	TDF	Discontinue TDF and give supportive treatment. After clinical resolution, resume ART, replacing the offending drug.
Peripheral neuropathy	d4T* and ddI	Consider replacement by an NRTI with minimal or no neurotoxicity (AZT, TDF, or ABC). Symptomatic treatment should be considered.

\* Phasing out of d4T recommended by WHO.

infected adult with a CD4 count less than 350 cells/ $\mu$ L or with the same clinical criteria (WHO stage 2, 3, or 4) (Table 115.5).

### Immune Reconstitution Inflammatory Syndrome (IRIS)

The term “immune reconstitution inflammatory syndrome” (IRIS) describes a collection of inflammatory disorders associated with paradoxical worsening of preexisting infectious processes following the initiation of highly active antiretroviral therapy (HAART) in HIV-infected individuals. Preexisting infections in individuals with IRIS may have been previously diagnosed and treated or they may be subclinical and later unmasked by the host's regained

capacity to mount an inflammatory response. The clinical signs and symptoms and management principles are summarized in the Table 115.6.

### ART for Women of Childbearing Potential or Who are Pregnant

Decision to use antiretroviral agents to be used in women of child bearing age group depends on the medical need for ART for the women herself or as an antiretroviral prophylaxis to prevent transmission to the child (Table 115.7). ART is recommended for pregnant women according to the same eligibility criteria as for non-pregnant adults.

Women with WHO clinical stage 3 disease and CD4 count less than 350 cells/ $\mu$ L should initiate ART. EFV should be



**Table 115.5** Summary of Cotrimoxazole Prophylaxis in HIV Infected Adults

	CD4 not available	CD4 available*
When to commence primary cotrimoxazole prophylaxis	WHO clinical stage 2, 3, 4, (including all patients with TB)	Any WHO clinical stage and CD4 less than 200 cells/ $\mu$ L where the aim of cotrimoxazole prophylaxis is the prevention of PCP and toxoplasmosis. Any WHO clinical stage and CD4 less than 350 cells/ $\mu$ L where the aim of cotrimoxazole prophylaxis is the reduction of morbidity and mortality associated with malaria, bacterial diarrheal disease and bacterial pneumonias in addition to the prevention of PCP and toxoplasmosis
Commencing secondary cotrimoxazole prophylaxis	Secondary prophylaxis is recommended for all patients who have completed successful treatment for PCP	
Timing the initiation of cotrimoxazole in relation to initiating ART	Start cotrimoxazole prophylaxis first Start ART two weeks later if the individual is tolerating co-trimoxazole and has no symptoms of allergy (rash, hepatotoxicity) A two week separation will assist clinical management where the cause of the symptoms maybe either cotrimoxazole or ART (especially if starting nevirapine containing regimen)	
Dosing	One double strength tablet or two single strength tablets once daily Total daily dose is 960 mg (800 mg SMZ + 160 mg TMP)	
Cotrimoxazole in pregnant women	Women who fulfill the criteria for cotrimoxazole prophylaxis should continue on it throughout their pregnancy <sup>6</sup> If a woman requires cotrimoxazole prophylaxis during pregnancy, it should be started regardless of the stage of pregnancy <sup>7</sup> Breastfeeding women should continue to receive cotrimoxazole prophylaxis	
Patients allergic to sulpha-based medications	Dapsone 100 mg per day, if available Cotrimoxazole desensitization may be attempted but not in patients with a previous severe reaction to CTX or other sulpha containing drugs.	
Monitoring	No specific laboratory monitoring is required in patients receiving cotrimoxazole	
When to stop cotrimoxazole prophylaxis in patients on ART	CD4 count not available	CD4 count available
	<b>Option 1</b> Continue prophylaxis indefinitely <b>Option 2</b> Consider discontinuation in patients after one year on ART without WHO stage 2, 3 or 4 events, good adherence and secure access to ART	CD4 count greater than 200 or greater than 350 cells/ $\mu$ L, (depending on choice of CD4 starting level) for 6 months on ART <sup>8,9</sup>

\* Commence primary cotrimoxazole prophylaxis in the two situations described under the heading when CD4 available.

**Table 115.6** Clinical Features and Management of Immune Reconstitution Inflammatory Syndrome

Definition	A collection of signs and symptoms resulting from the ability to mount an immune response associated with immune recovery on ART. <sup>10</sup>
Frequency	10% of all patients initiating ART Up to 25% among patients initiating ART with a CD4 cell count less than 50 cells/ $\mu$ L. <sup>6,11,12</sup>
Timing	Typically within 2–12 weeks of initiation of ART but may present later
Signs and symptoms	Unexpected deterioration of clinical status soon after commencing ART Unmasking of subclinical infections such as TB, which present as new active disease Worsening of co-existing infections such a flare of hepatitis B or C
Most common IRIS events	60% of IRIS events are <i>M. tuberculosis</i> , MAC or cryptococcal disease <sup>13</sup>
Other reported IRIS events	Toxoplasmosis, cytomegalovirus, lymphoma, Herpes zoster and herpes simplex, human papilloma virus, molluscum contagiosum, psoriasis eczema, hepatitis B or C flare, sarcoidosis, Graves disease, Guillain-Barré Syndrome
Principles of Management	IRIS may be mild and resolve without treatment. Continue ART if possible Diagnose and treat the specific pathogen in order to decrease the antigen load. Consider corticosteroids in moderate to severe cases of IRIS. Prednisolone (or prednisone) at 0.5 mg/kg/day orally or IV for five to ten days or longer depending on the severity of the inflammation Discontinue ART and prioritize treatment of the pathogen in patients who are severely unwell Aspiration and drainage of lymph nodes and abscesses (may need to be repeated several times) Emergency surgical decompression in cases of tracheal or intestinal obstruction

discontinued and replaced with another drug as it is potentially teratogenic.

In other situations ART may be used as prophylaxis, when mother is not in need herself to prevent MCT and during breastfeeding.

## ART in Tuberculosis/HIV Co-infection

The intersection of the HIV and TB epidemics has led to a dramatic upsurge in global TB incidence, resulting in remarkable increase in morbidity and mortality in some

**Table 115.7** Initiating ART in Women during Pregnancy and Breastfeeding

Clinical Situation	Guiding principles	Recommendations
All women	Treatment decisions are based solely on the women's medical need	Recommended first-line regimen is a NVP-based plus 2 NRTIs. EFV plus 2 NRTIs may be used if women have access to consistent and reliable barrier methods of contraception or after the first trimester of pregnancy
Initiating ART in pregnant women	ART is recommended for pregnant women according to the same eligibility criteria as for non-pregnant adults Women with WHO clinical stage 3 disease and CD4 count less than 350 cells/mL should initiate ART	Recommended regimen is 2 NRTIs plus a NNRTI. The preferred regimen is AZT + 3TC + NVP with careful monitoring of women with higher CD4 counts (>250).
Women who are pregnant, are in the first trimester and are taking EFV	EFV should be discontinued and replaced with another drug	NVP is substituted for EFV with close monitoring in women with higher CD4 counts. Alternatively a PI-based or a triple NRTI regimen could be substituted
Women who are breastfeeding	ART is recommended for postpartum breastfeeding women who meet the WHO criteria for initiation of therapy for their own health	The preferred regimen is AZT + 3TC + NVP
Women who received ART as part of PMCT intervention	Women who have previously received single-dose NVP prophylaxis for prevention of MTCT should be considered eligible for NNRTI-based regimens. Alternatives may be considered for women whose exposure to single dose NVP (Sd-NVP) was <6 months before ART was initiated	Sd-NVP more than 6 months, NNRTI-based regimen. Sd-NVP <6 months, A triple NRTI regimen or PI-based regimen also can be considered

parts of the world. HIV-infected patients are at increased risk of developing active TB from both reactivated latent and exogenous infection. HIV infection is also a risk factor for accelerated progression of TB following exposure, which has resulted in outbreaks of multidrug-resistant and extensively drug-resistant (XDR) tuberculosis.

Initiating ART in patients with active TB is also guided by the CD4 count and is initiated at least 2 weeks after the initiation of treatment for tuberculosis as shown in Box 115.1. Choice of NRTI is the same as for all patients. Preferred NRTIs in first-line regimens are zidovudine or tenofovir. Alternatives are stavudine or abacavir. Efavirenz is the preferred NNRTI. Despite EFV blood levels being decreased in the presence of rifampicin, the standard 600 mg dose is recommended.<sup>14–18</sup> Patients receiving nevirapine-based ART should be switched to efavirenz while taking rifampicin. Switching back to NVP after

rifampicin is completed can be considered. When switching back from EFV to NVP no lead-in dose is required. If a pregnant woman develops active TB and she is in the second or third trimester, an EFV containing ART regimen can be considered. An alternative in women with active TB in the first trimester is a triple NRTI regimen or a NVP containing regimen, with careful monitoring in women with higher CD4 counts or when CD4 count is unknown.

### ART Failure and When to Switch Therapy

ART failure can be diagnosed on clinical, immunological or virological criteria (Table 115.8). In resource limited settings, viral load testing is often unavailable and clinical and/or immunological criteria are normally used. Failure is never defined in the first 6 months following initiation of ART. Clinical events that occur before the first 6 months of therapy often represent IRIS and not failure. ART failure necessitates change to second line or PI based regimen (Table 115.9). The second line ARVs are more toxic and warrant stringent monitoring. Table 115.10 summarizes common toxicities of second line agents and their management.

### Protease Inhibitor (PI) Component

A ritonavir-boosted PI (PI/r) is the backbone of all second-line regimens. WHO preferred PIs are:

- LPV/r (KALETRA®). New heat stable tablets (also marketed in resource limited countries as ALLUVIA®) are becoming increasingly available and do not require refrigeration
- ATV/r. ARV does not require refrigeration but require boosting with RTV which still needs refrigeration. Generic heat stable RTV tablets will become available soon

**Box 115.1** Initiating ART in Patients with Active TB

CD4 Cell Count	ART recommendations	Timing of ART in relation to the start of TB treatment
CD4 less than 200/ $\mu$ L	Recommend ART	Between 2 and 8 weeks
CD4 between 200 less than 350/ $\mu$ L	Recommend ART	After 8 weeks
CD4 greater 350/ $\mu$ L	Defer ART	Re-evaluate patient at 8 weeks and at the end of TB treatment
CD4 not available	Recommend ART	2–8 weeks

**Table 115.8:** Criteria for ART Failure

<b>Clinical failure</b>	New or recurrent WHO stage 4 condition after at least 6 months on ART
<b>Immunological failure</b>	<p><b>Pattern 1</b> CD4 count less than 100 cells/<math>\mu</math>L (some experts recommend <math>&lt;50</math> cells/<math>\mu</math>L) after one year of therapy</p> <p><b>Pattern 2</b> Return to or a fall below the pre-therapy CD4 baseline after one year of therapy</p> <p><b>Pattern 3</b> 50% decline from the on-treatment peak CD4 value (if known). CD4 cell count can also be used to determine when not to switch therapy. For example, in a patient with a new clinical stage 3 event for whom switch is being considered switching is not to be recommended if the CD4 cell count is greater than 200 cells/<math>\mu</math>L.</p>
<b>Virological failure</b>	Viral load greater than 10,000 copies/mL after at least 6 months on ART

**Table 115.9:** Choice of Second-Line Regimens for Treatment Failure<sup>19</sup>

First-line regimen		Second-line regimen	
		RTI component*	PI component
Preferred regimens	AZT + 3TC + (NVP or EFV)	TDF + 3TC	PI/r
	TDF + 3TC + (NVP or EFV)	AZT + 3TC	
Alternative regimen	d4T* + 3TC + (NVP or EFV)	TDF + 3TC	

\*The entire treatment regimen needs to be changed in the setting of treatment failure.

**Table 115.10:** Symptom Directed Toxicity Management for Second-Line ARVs

Toxicity	Causative ARVs	Recommendations
Dyslipidemia	PIs	Cholesterol and Triglyceride elevations to grade 1 or 2 Monitor, diet, exercise Cholesterol and Triglyceride elevations to grade 3 or 4 Treat elevated Triglycerides with fibrates (fenofibrate 600 mg 1–2 times per day) Treat elevated Cholesterol with statins. Avoid simvastatin due to interactions with PIs (Annexure 2)
GI intolerance	All ARVs	Usually self-limited, without need to discontinue ART. Symptomatic treatment should be offered.
Hematological toxicities (particularly anemia and leukopenia)	AZT	If severe (Hb $<6.5$ ), stop AZT and consider blood transfusion.
Hepatic dysfunction	LPV/r and other PIs less commonly	If ALT $>5$ -fold the basal level, discontinue ART and monitor. After resolution, try a different PI
Hyperbilirubinemia (indirect)	ATV	Generally asymptomatic, but can cause scleral icterus (without ALT elevations). Replace ATV or IDV with another PI.
Lactic acidosis	All NRTIs (particularly d4T* and ddI)	Discontinue ART and give supportive treatment. After clinical resolution, resume ART, replacing the offending ITRN. ABC, TDF, and 3TC are less likely to cause this type of toxicity.
Lipoatrophy and lipodystrophy	All NRTIs (particularly d4T*) and PIs	Early replacement of the suspected ARV drug.
Renal toxicity (renal tubular dysfunction)	TDF	Discontinue TDF and give supportive treatment. After clinical resolution, resume ART, replacing the offending drug.

\*Phasing out of d4T recommended by WHO.

Unboosted PIs are not recommended with the exception of NFV if no ritonavir is available. Nelfinavir is less potent than a boosted PI.<sup>20,21</sup> Second-line ARVs sometimes are more likely to produce serious side effects that need urgent attention.

## HIV Infection in Children

### LABORATORY DIAGNOSIS

#### Viral Diagnostic Assays

HIV infection can be definitively diagnosed using viral diagnostic assays (detection of HIV by DNA or RNA polymerase chain reaction [PCR]).<sup>22,23</sup> These assays may not be available in resource limited settings. If available, virological testing should be performed after 6–8 weeks in non-breastfed infants. In breastfed infants, testing should be performed between 6 weeks and 6 months to allow optimal infant feeding counseling, or 6 weeks after complete cessation of breastfeeding. HIV infection is diagnosed by two positive HIV virologic tests performed on separate blood samples.

#### HIV Antibody Testing

In the absence of viral diagnostic assays, HIV antibody testing is used. However, the diagnosis of HIV infection in infants and children by HIV antibody testing is complicated by the persistence of maternal antibodies in children up to 18 months of age. Breastfeeding infants are at risk of HIV infection during



the period of breastfeeding and a negative virologic or antibody test during the breastfeeding period does not exclude the child becoming infected at a later date. Testing is recommended at any time 6 weeks after complete cessation of breastfeeding. Two or more negative HIV antibody tests performed at age 9–12 months with an interval of at least 1 month between the tests also can be used to reasonably exclude HIV infection among non-breastfed children with no clinical evidence of HIV infection. HIV infection can be definitively excluded if the HIV antibody is negative at age 18 months. A persistent HIV positive test result after 18 months post delivery confirms HIV infection regardless of breastfeeding.<sup>24</sup>

### INFANT FEEDING COUNSELING<sup>25–28</sup>

- Explain risk of HIV transmission through breastfeeding and implications of mixed feeding. Specifically, explain that mixed feeding results in more HIV transmission than exclusive breastfeeding.
- Ensure mothers and family members understand the need to balance the competing risks of reducing the risk of HIV to infants through breastfeeding with the need for minimizing the risk of other causes of morbidity and mortality through not breastfeeding
- Provide counseling and information about the risks and benefits of various infant feeding options based on locally feasible and acceptable feeding practices
- Recommend avoidance of all breastfeeding if replacement feeding is acceptable, feasible, affordable, sustainable and safe. Otherwise, recommend exclusive breastfeeding during the first months of life and support mothers to safely use replacement feeding when it becomes feasible for them. It is always important to ensure that children less than six months who are not breastfed have uninterrupted access to nutritionally adequate breast-milk substitutes that are safely prepared.

### COTRIMOXAZOLE PROPHYLAXIS<sup>29</sup>

In resource-limited settings, cotrimoxazole prophylaxis is recommended for all HIV-exposed infants starting at 4–6 weeks of age (or at first encounter with the healthcare system) and continued until HIV infection can be excluded (Table 115.11). Cotrimoxazole is also recommended for HIV-exposed breastfeeding children of any age and cotrimoxazole prophylaxis should be continued until HIV infection can be excluded by HIV antibody testing (beyond 18 months of age or older) or virological testing (younger than 18 months of age) following at least six weeks after complete cessation of breastfeeding. The risk of PCP is greatest in the first 6 months of life. All children under one year of age with **documented** HIV infection should receive cotrimoxazole prophylaxis regardless of symptoms or CD4 percentage. Beyond the age of one year,

**Table 115.11:** Cotrimoxazole Prophylaxis for HIV-Exposed Infants and Children

HIV-exposed infants & children*	Situation		
	Confirmed HIV infected infants and children†		
	under 1 yr	1–4 yr‡	5 yr and older
<b>Cotrimoxazole prophylaxis is universally indicated, starting at four to six weeks after birth and maintained until cessation of risk of HIV transmission and exclusion of HIV infection.</b>	Cotrimoxazole prophylaxis is indicated regardless of CD4 percent or clinical status.	WHO stages 2, 3 and 4 regardless of CD4 percent OR Any WHO stage and CD4 less than 25%	Follow adult recommendations

**Universal option:** Prophylaxis for all infants and children born to confirmed or suspected HIV infected mothers. This strategy may be considered in settings with high prevalence of HIV, high infant mortality due to infectious diseases and limited health infrastructure.

\* Defined as a child born to an HIV-infected mother or child breastfeeding from an HIV-infected mother until HIV exposure stops (6 weeks after complete cessation of breastfeeding) and infection can be excluded

† In children under 18 months HIV infection can only be confirmed by virological testing.

‡ Once started on CTX it should continue until 5 years regardless of clinical symptoms or CD4 percentage. Specifically, infants who begin CTX prophylaxis before the age of one year and who subsequently are asymptomatic and/or have CD4 levels 25% or greater should remain on CTX prophylaxis until they reach 5 years of age.

initiation of cotrimoxazole prophylaxis is recommended for symptomatic children (WHO stages 2, 3, or 4) or children with CD4 less than 25%.<sup>30</sup> All children who commence cotrimoxazole prophylaxis (irrespective of whether cotrimoxazole was initiated in the first year of life or after that) should continue until the age of 5 years when they can be reassessed. Adult clinical staging and CD4 count thresholds for cotrimoxazole initiation or discontinuation apply for children older than five years of age.<sup>31</sup>

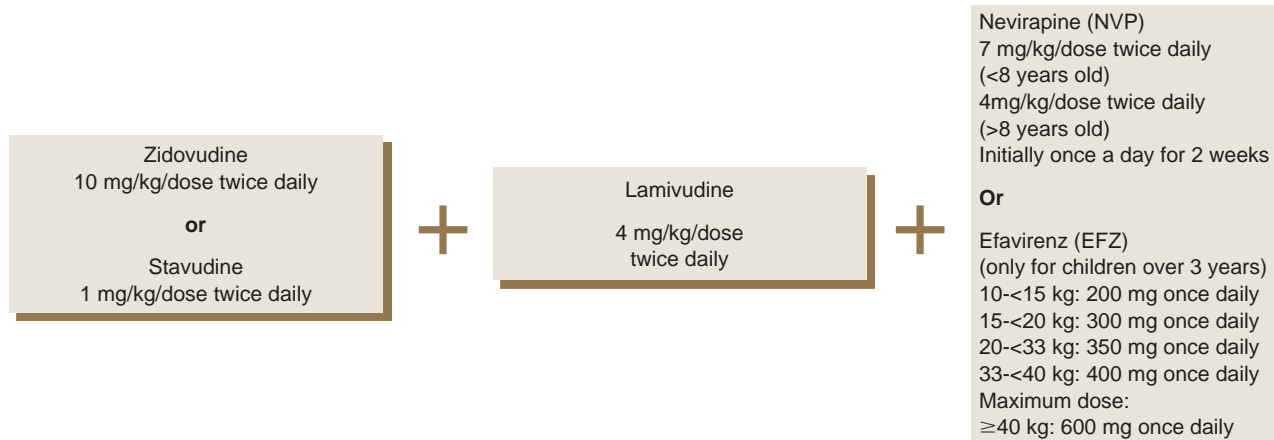
In children with **presumptive symptomatic** HIV disease, cotrimoxazole prophylaxis should be started at any age and continued until HIV infection status can be excluded.

### STARTING ART

The WHO clinical and immunological staging is given in Annexure 3. Initiation of ART is based both on the clinical as well as the immunological disease. The available pediatric drugs and formulations are given in Annexure 4.

Indications for initiating ART in infants and children

- WHO stage 3 or 4 in children with confirmed HIV infection.

**Box 115.2** WHO Recommended First-Line Antiretroviral Regimens for Children

- CD4 cell count suggestive of severe immunosuppression with confirmed HIV infection.
- WHO stage 3 or 4 and presumptive diagnosis of HIV infection in children younger than 18 months of age.

Recommended first-line ART regimens: Box 115.2.

**CHANGING THERAPY DUE TO CLINICAL FAILURE****Clinical Failure**

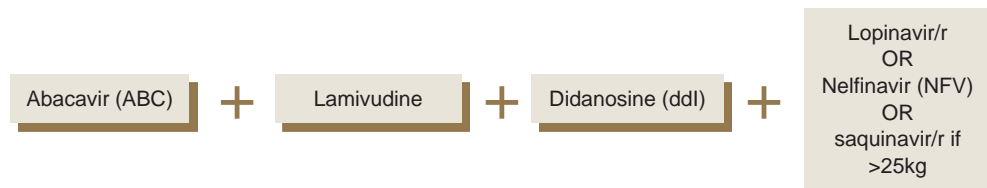
Clinical signs of drug failure in children include:

- lack of growth among children who show an initial response to treatment
- decline in growth among children who show an initial growth response to therapy
- a loss of neuro-developmental milestones or the development of encephalopathy
- occurrence of new opportunistic infections or malignancy signifying clinical disease progression (as distinguished from immune reconstitution syndrome, which can occur in the first three months following the initiation of ARV, and does not signify treatment failure).
- recurrence of infections, such as oral candidiasis, that are refractory to treatment

Before an ARV regimen is thought to be failing based on clinical criteria, the child should have had a reasonable trial on the therapy (e.g., have received the regimen for at least 24 weeks). Failure of therapy may be due to poor adherence.<sup>32,33</sup> Counsel to address adherence issues if this is the case and do not change the regimen.

**Immunological Failure**

Providing the child is adherent to the therapy, immunological failure is defined as a return in CD4 cell percent (or for children older than 6 years of age, absolute CD4 cell count) to pre-therapy baseline or below, in the absence of other concurrent infection to explain transient CD4 decrease, or a greater than 50% fall from peak level on therapy of CD4 cell percentage (or for children older than 6 years of age, absolute CD4 cell count) in the absence of other concurrent infection to explain transient CD4 decrease. A rapid CD4 decrease (greater than 30% over 6 months) also may indicate immunological failure. Change to second line antiretroviral therapy is recommended if the first line therapy has failed. PI based regimen with three NRTIs is recommended (Box 115.3).

**Box 115.3** Second-Line Treatment Regimen for Children

## Prevention of Mother-to-Child Transmission (PMCT)

### COUNSELING

Counseling is an essential part of PMCT programs to provide informed choice so that pregnant women are able to decide on:

- HIV testing
- Choosing ART treatment or ARV prophylaxis, with commitment to good adherence
- safe delivery options
- appropriate infant feeding practice

Another important aspect is that PMCT can be a useful means for HIV prevention as HIV-negative pregnant mothers can be thoroughly counseled to maintain their negative status, and their spouses should also be encouraged for testing.

### SAFE DELIVERY

Interventions that reduce MTCT risk in labor and delivery include:

- Universal precautions
- Minimal use of cervical examinations
- Avoidance of:
  - Prolonged labor
  - Routine rupture of membranes
  - Unnecessary trauma such as episiotomies and fetal scalp monitoring
- Minimize risk of postnatal hemorrhage
- Safe transfusion practices

Elective caesarean section, when performed before the onset of labor or membrane rupture, has been associated with reduced MTCT. But it needs to be considered individually, the benefits and risks of vaginal delivery versus elective caesarean section, including the safety of the blood supply and the risk of complications from operation.

### ARV PROPHYLAXIS FOR PMCT

ARV prophylaxis for prevention of MCT has been summarized in Table 115.12; refer Table 115.13 for doses of prophylactic ARVs.

### Conclusions

Predominant contribution to the global HIV comes from sub Saharan Africa and Central Asia and management of HIV infection in these resources limited settings, is a challenge. However, with universal access to HAART and effective healthcare programmers, control of HIV infection is now a realistic public health goal. Effective treatment guidelines for prevention of mother to child infection and universal management of individuals with HIV infection and their monitoring has successfully altered outcome in people living with HIV and AIDS. It is no longer a fatal disease but a chronic manageable condition.

**Table 115.12:** ARV Prophylaxis for Prevention of Mother-to-Child Transmission of HIV

Ranking	Time of administration		
	Pregnancy	Labor	Postpartum
<b>Recommended</b>	AZT (>28 weeks gestation)	Sd-NVP* + AZT/3TC	<b>Mother:</b> AZT/3TC × 7 days* <b>Infant:</b> Sd-NVP* + AZT × 7 days†
<b>Alternative</b>	AZT (>28 weeks gestation)	Sd-NVP	<b>Infant:</b> Sd-NVP + AZT × 7 days†
<b>Minimum</b>	-	Sd-NVP + AZT/3TC	<b>Mother:</b> AZT/3TC × 7 days <b>Infant:</b> Sd-NVP
<b>Minimum</b>	-	Sd-NVP	<b>Infant:</b> Sd-NVP

\*If the woman receives at least four weeks of AZT during pregnancy, omission of the NVP dose for mothers may be considered. In this case the NVP dose must be given to the infant immediately after birth, AZT is recommended for four weeks instead of one week, and the mother will not require 3TC during labor as well as AZT and 3TC postpartum.

†If the mother receives less than four weeks of AZT during pregnancy, AZT is recommended for four weeks instead of one week.

**Table 115.13:** Doses of Antiretroviral Prophylaxis Drugs for Prevention of Mother-to-Child Transmission

#### For Mothers

##### During pregnancy

- AZT 300 mg twice a day starting at 28 weeks or as soon as possible thereafter

##### During labor

- Sd-NVP 200 mg at onset of labor
- AZT 600 mg at onset of labor OR 300 mg at onset of labor and every 3 hours until delivery
- 3TC 150 mg at onset of labor and every 12 hours until delivery.

##### After delivery

- AZT 300 mg twice a day for 7 days
- 3TC 150 mg twice a day for 7 days

#### For Infants

- Sd-NVP: 2 mg/kg oral suspension (or 6 mg) at once immediately after birth (within 72 hours)
- AZT 4 mg/kg twice a day for 7 days OR 4 weeks\*
- 3TC 2 mg/kg twice a day for 7 days

\* If the mother receives less than four weeks of AZT during pregnancy, AZT is recommended for 4 weeks instead of one week.

## Annexures

### Annexure 1: WHO Clinical Staging of HIV Disease in Adults and Adolescents

The revised WHO clinical classification of HIV-associated disease is designed to be used in patients with **confirmed HIV infection**.



Along with CD4 count testing, where available, the staging system is used to guide decisions on when to start opportunistic infection (OI) prophylaxis and when to start and switch ART.

Clinical stage 1 (Asymptomatic)
Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2 (Mild disease)
Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infections
Clinical stage 3 (Moderate disease)
Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhea for longer than one month Unexplained persistent fever (intermittent or constant for longer than one month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anemia (<8 g/dl), neutropenia (<0.5 × 10 <sup>9</sup> /L) and or chronic thrombocytopenia (<50 × 10 <sup>9</sup> /L <sup>3</sup> )
Clinical stage 4 (Severe disease)
HIV wasting syndrome <i>Pneumocystis jiroveci</i> pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection Oesophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Extrapulmonary cryptococcosis including meningitis Disseminated non-tuberculous mycobacterial infection Progressive multifocal leukoencephalopathy Penicilliosis Chronic cryptosporidiosis Chronic isosporiasis Disseminated mycosis (extrapulmonary histoplasmosis, coccidiomycosis) Recurrent septicemia (including non-typhoidal <i>Salmonella</i> ) Lymphoma (cerebral or B cell non-Hodgkin) Invasive cervical carcinoma Atypical disseminated leishmaniasis Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

Source: Revised WHO Clinical Staging and Immunological Classification of HIV and case definition of HIV for surveillance, May 2006.

## Annexure 2: Dosages of Antiretroviral Drugs for Adults and Adolescents

Generic name	Dose	
<b>Nucleoside RTIs</b>		
Abacavir (ABC)	300 mg twice daily or 600 mg once daily	
Zidovudine (AZT)	250 mg or 300 mg twice daily	
Emtricitabine (FTC)	200 mg once daily	
Didanosine (ddI)	>60 kg: 400 mg once daily	
buffered tabs or enteric coated (EC) caps	<60 kg: 250 mg once daily	
Lamivudine (3TC)	150 mg twice daily or	
Stavudine (d4T)*	300 mg once daily	
	30 mg twice daily irrespective of weight	
<b>Nucleotide RTIs</b>		
Tenofovir	300 mg once daily	
	Creatinine clearance < 50 mL/min 300 mg alternate days	
<b>Non-nucleoside RTIs</b>		
Efavirenz (EFV)	600 mg once daily	
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily	
<b>Proteases inhibitors</b>		
Atazanavir/ritonavir (ATV/r)	300 mg/100 mg once daily	
Indinavir/ritonavir (IDV/r)	800 mg/100 mg twice daily	
Lopinavir 133.3 mg + ritonavir 33.3 mg	Capsule	Three capsules twice daily (400/100mg twice daily)
		four capsules twice daily when combined with EFV or NVP (533/133,33 mg twice daily)
Lopinavir/ritonavir (LPV/r)	Tablet (heat stable formulation)	Treatment naïve patients
	Lopinavir 200 mg + ritonavir 50 mg	Two tablets twice daily irrespective of coadministration with EFV or NVP (400/100 mg twice daily)
		Treatment experienced patients
		Three tablets twice daily when combined with EFV or NVP (600/150 mg twice daily)

\* Phasing out of d4T recommended by WHO.

### Annexure 3: Revised WHO Clinical Staging of HIV/AIDS for Infants and Children with Established HIV Infection

The clinical staging system is designed for use where HIV infection is confirmed by HIV antibody or virological testing.

#### Primary HIV infection

Asymptomatic  
Acute retroviral syndrome

#### Clinical Stage 1

Asymptomatic  
Persistent generalized lymphadenopathy

#### Clinical Stage 2

Unexplained persistent hepatosplenomegaly  
Papular pruritic eruptions  
Extensive wart virus infection  
Extensive molluscum contagiosum  
Recurrent oral ulcerations  
Unexplained persistent parotid enlargement  
Linear gingival erythema  
Herpes zoster  
Recurrent or chronic upper respiratory tract infections (otitis media, otorrhea, sinusitis, tonsillitis )  
Fungal nail infections

#### Clinical Stage 3

Moderate unexplained malnutrition not adequately responding to standard therapy  
Unexplained persistent diarrhea (14 days or more )  
Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month)  
Persistent oral candida (outside first 6–8 weeks of life)  
Oral hairy leukoplakia  
Acute necrotizing ulcerative gingivitis/periodontitis  
Lymph node TB  
Pulmonary tuberculosis  
Severe recurrent presumed bacterial pneumonia  
Symptomatic lymphoid interstitial pneumonitis  
Chronic HIV-associated lung disease including bronchiectasis  
Unexplained anemia (<8g/dl ), neutropenia (<500/mL) or chronic thrombocytopenia (<50 000/μL)  
HIV-associated cardiomyopathy or HIV-associated nephropathy

#### Clinical Stage 4

Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy  
Pneumocystis pneumonia  
Recurrent severe presumed bacterial infections  
(e.g., empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)  
Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)  
Extrapulmonary tuberculosis  
Kaposi sarcoma  
Oesophageal candidiasis (or candida of trachea, bronchi or lungs)  
Central nervous system toxoplasmosis (outside the neonatal period)  
HIV encephalopathy  
Cytomegalovirus (CMV) retinitis or CMV infection affecting another organ, with onset at age >1 month  
Extrapulmonary cryptococcosis including meningitis  
Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis, penicilliosis)  
Chronic cryptosporidiosis  
Chronic isosporiasis  
Disseminated non-tuberculous mycobacterial infection  
Acquired HIV-associated rectal fistula  
Cerebral or B cell non-Hodgkin lymphoma  
Progressive multifocal leukoencephalopathy

## Annexure 4: Pediatric Drug Formulations and Doses of ARVs

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
<b>Nucleoside analogue reverse transcriptase inhibitors</b>				
<b>Zidovudine (ZDV)</b>	Syrup: 10 mg/mL Capsules: 100 mg; 250 mg Tablet: 300 mg	All ages	<4 weeks: 4 mg/kg/dose twice daily 4 weeks to 13 yrs: 180 mg/m <sup>2</sup> /dose twice daily Maximum dose: ≥13 yrs: 300 mg/dose twice daily	Large volume of syrup not well tolerated in older children, Syrup needs storage in glass jars and is light sensitive Can give with food Doses of 600 mg/m <sup>2</sup> /dose per day required for HIV encephalopathy Capsule can be opened and contents dispersed or tablet crushed and contents mixed with small amount of water or food and immediately taken (solution is stable at room temperature) Do not use with d4T* (antagonistic antiretroviral effect)
<b>Lamivudine (3TC)</b>	Oral solution: 10 mg/mL Tablet: 150 mg	All ages	<30 days: 2 mg/kg/dose twice daily ≥30 days or <60 kg: 4 mg/kg/dose twice daily Maximum dose: >60 kg: 150 mg/dose twice daily	Well tolerated Can give with food Store solution at room temperature (use within one month of opening) Tablet can be crushed and contents mixed with small amount of water or food and immediately taken
<b>Fixed-dose combination of ZDV plus 3TC</b>	No liquid available Tablet: 300 mg ZDV plus 150 mg 3TC	Adolescents and adults	Maximum dose: >13 yrs or >60 kg: 1 tablet/dose twice daily (should not be given if <30 kg weight)	Ideally, tablet should not be split Tablet can be crushed if required and contents mixed with small amount of water or food and immediately taken At weight <30 kg, ZDV and 3TC cannot be dosed accurately in tablet form
<b>Stavudine (d4T)*</b>	Oral solution: 1 mg/mL Capsules: 15 mg, 20 mg, 30 mg, 40 mg	All ages	< 30 kg: 1 mg/kg/dose twice daily 30 to 60 kg: 30 mg/dose twice daily Maximum dose: > 60 kg: 40 mg/dose twice daily	Large volume of solution Keep solution refrigerated; stable for 30 days; must shake well. Needs to be stored in glass bottles. Capsules can be opened up and mixed with small amount of food or water (stable in solution for 24 hours if kept refrigerated) Do not use with ZDV (antagonistic antiretroviral effect)
<b>Fixed dose combination of d4T* plus 3TC</b>	No liquid available Tablet: d4T 30 mg plus 3TC 150 mg; d4T 40 mg plus 3TC 150 mg	Adolescents and adults	Maximum dose: 30–60 kg: one 30 mg d4T-based tablet twice daily ≥60 kg: one 40 mg d4T-based tablet twice daily	Ideally, tablet should not be split See comments under individual drug components
<b>Didanosine (ddI)</b>	Oral suspension pediatric powder/ water: 10 mg/mL. In many countries needs to be made up with additional antacid Chewable tablets: 25 mg; 50 mg; 100 mg; 150 mg; 200 mg Enteric-coated beadlets in capsules: 125 mg; 200 mg; 250 mg; 400 mg	All ages	< 3 mos: 50 mg/m <sup>2</sup> /dose twice daily 3 mos to < 13 yrs: 90–120 mg/m <sup>2</sup> /dose twice daily or 240 mg/m <sup>2</sup> /dose once daily Maximum dose: ≥13 yrs or > 60 kg: 200 mg/dose twice daily or 400 mg once daily	Keeps suspension refrigerated; stable for 30 days; must shake well Administer on empty stomach, at least 30 minutes before or 2 hours after eating If tablets dispersed in water, at least 2 of appropriate strength tablets should be dissolved for adequate buffering Enteric-coated beadlets in capsules can be opened and sprinkled on small amount of food



Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
<b>Abacavir (ABC)</b>	Oral solution: 20 mg/mL Tablet: 300 mg	Over age 3 months	<16 yrs or <37.5 kg: 8 mg/kg/dose twice daily Maximum dose: >16 yrs or ≥37.5 kg: 300 mg/dose twice daily	Can give with food Tablet can be crushed and contents mixed with small amount water or food and immediately ingested MUST WARN PARENTS ABOUT HYPERSENSITIVITY REACTION ABC should be stopped permanently if hypersensitivity reaction occurs
<b>Fixed-dose combination of ZDV plus 3TC plus ABC</b>	No liquid available Tablet: ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg	Adolescents and adults	Maximum dose: > 40 kg: 1 tablet/dose twice daily	Ideally, tablet should not be split At weight <30 kg, ZDV/3TC/ABC cannot be dosed accurately in tablet form MUST WARN PARENTS ABOUT HYPERSENSITIVITY REACTION ZDV/3TC/ABC should be stopped permanently if hypersensitivity reaction occurs
<b>Non-nucleoside reverse transcriptase inhibitors</b>				
<b>Nevirapine (NVP)</b>	Oral suspension: 10 mg/mL Tablet: 200 mg	All ages	15–30 days: 5 mg/kg/dose once daily x 2 weeks, then 120 mg/m <sup>2</sup> /dose twice daily x 2 weeks, then 200 mg/m <sup>2</sup> /dose twice daily >30 days to 13 yrs: 120 mg/m <sup>2</sup> /dose once daily for 2 weeks, then 120–200 mg/m <sup>2</sup> /dose twice daily Maximum dose: >13 yrs: 200 mg/dose once daily for first 2 weeks, then 200 mg/dose twice daily	If rifampicin co-administration, avoid use (see Tuberculosis section) Store suspension at room temperature; must shake well Can give with food Tablets are scored and can be divided into two equal halves to give a 100 mg dose; can be crushed and combined with small amount of water or food and immediately administered MUST WARN PARENTS ABOUT RASH Do not escalate dose if rash occurs (if mild/moderate rash, hold drug; when rash cleared, restart dosing from beginning of dose escalation; if severe rash, discontinue drug) Drug interactions
<b>Efavirenz (EFV)</b>	Syrup: 30 mg/mL (note: syrup requires higher doses than capsules, see dosing chart) Capsules: 50 mg, 100 mg, 200 mg	Only for children over 3 yrs	Capsule (liquid ) dose for > 3 yrs: 10 to 15 kg: 200 mg (270 mg = 9 mL) once daily 15 to < 20 kg: 250 mg (300 mg = 10 mL) once daily 20 to < 25 kg: 300 mg (360 mg = 12 mL) once daily 25 to < 33 kg: 350 mg (450 mg = 15 mL) once daily 33 to < 40 kg: 400 mg (510 mg = 17 mL) once daily Maximum dose: ≥ 40 kg: 600 mg once daily	Capsules may be opened and added to food but have very peppery taste; however, can mix with sweet foods or jam to disguise taste Can give with food (but avoid after high fat meals which increase absorption by 50%) Best given at bedtime, especially in the first 2 weeks, to reduce central nervous system side effects Drug interactions
<b>Fixed-dose combination of *d4T plus 3TC plus NVP</b>	No liquid available Tablet: 30 mg d4T/150 mg 3TC/200 mg NVP; 40 mg d4T/150 mg 3TC/200 mg NVP	Adults and adolescents	Maximum dose: 30–60 kg: one 30 mg d4T-based tablet twice daily ≥60 kg: one 40 mg d4T-based tablet twice daily	Ideally, tablet should not be split At weight <30 kg, d4T/3TC/NVP cannot be dosed accurately in tablet form; if tablets are split, NVP dose will be inadequate for very young children and additional NVP is needed to give total of 200 mg/m <sup>2</sup> /dose twice daily Since it contains NVP, requires dose escalation See comments under individual drug components

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
<b>Protease inhibitors</b>				
<b>Nelfinavir (NFV)</b>	Powder for oral suspension (mix with liquid): 200 mg per level teaspoon (50 mg per 1.25 mL scoop): 5 mL  Tablet: 250 mg (tablets can be halved; can be crushed and added to food or dissolved in water)	All ages  However, extensive pharmacokinetic variability in infants, with requirement for very high doses in infants < 1 yr	<1 yr: 50 mg/kg/dose three times daily or 75 mg/kg/dose twice daily >1 yr to <13 yrs: 55–65 mg/kg/dose twice daily  Maximum dose: ≥13 yrs: 1250 mg/dose twice daily	Powder is sweet, faintly bitter, but gritty and hard to dissolve; must be reconstituted immediately prior to administration in water, milk, formula, pudding, etc. – do not use acidic food or juice (increases bitter taste); solution stable for 6 hours  Because of difficulties with use of powder, use of crushed tablets preferred (even for infants) if appropriate dose can be given  Powder and tablets can be stored at room temperature  Take with food  Drug interactions (less than ritonavir-containing protease inhibitors)
<b>Lopinavir/ritonavir, (LPV/r)</b>	Oral solution: 80mg/mL Lopinavir plus 20 mg/mL ritonavir  Capsules: 133.3 mg Lopinavir plus 33.3 mg ritonavir	6 mo of age or older	> 6 mo to 13 yrs: 225 mg/m <sup>2</sup> LPV/57.5 mg/m <sup>2</sup> ritonavir twice daily or weight-based dosing: 7–15 kg: 12 mg/kg LPV/3 mg/kg ritonavir/dose twice daily 15–40 kg: 10 mg/kg lopinavir/5 mg/kg ritonavir twice daily  Maximum dose: > 40 kg: 400 mg LPV/100 mg ritonavir (3 capsules or 5 mL) twice daily	Preferably oral solution and capsules should be refrigerated; however, can store at room temperature up to 25°C (77°F) for 2 months; at temperature >25°C (77°F), drug degrades more rapidly  Liquid formulation has low volume but bitter taste  Capsules large  Capsules should <i>not</i> be crushed or opened, but must be swallowed whole  Should be taken with food  Drug interactions

\* Phasing out of d4T recommended by WHO.

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## Introduction

Perinatal transmission is the most important route of human immunodeficiency virus (HIV) infection in children. Most of pediatric HIV infection is preventable by providing antiretroviral treatment and antiretroviral (ARV) prophylaxis interventions. Prevention of infection is critically important since perinatal HIV transmission is associated with rapid clinical progression in infancy. In 2008, in low- and middle-income countries, 1.4 million HIV-infected women gave birth and an estimated 430,000 children were newly infected with HIV.<sup>1</sup> One of the landmark achievements in HIV research has been the observations of Pediatric AIDS Clinical Trials Group 076 (PACTG 076), which demonstrated reduction in the risk of perinatal transmission by nearly 70% with ARVs.<sup>2</sup> Since then significant progress has been made in prevention of mother-to-child transmission (PMTCT) of HIV both in high-burden as well as in the resource-limited settings. Now, for the first time, the elimination of mother-to-child transmission (MTCT) of HIV is considered a realistic public health goal and an important part of the campaign to achieve the millennium development goals. “A generation of children free from HIV infection is not impossible.”

## Global Scenario

Before 1990, pediatric HIV infection was a uniformly fatal disease, and MTCT rates without any interventions were reported to be around 15–40%. The interim analysis of PACTG 076 trial demonstrated that in pregnant women a regimen consisting of zidovudine (ZDV) given antepartum and intrapartum to mother and to newborn for 6 weeks reduces the risk of maternal-infant HIV transmission by approximately two-thirds.<sup>3–5</sup>

After the success of the PACTG 076 trial,<sup>2</sup> in the next decade, various clinical trials were initiated to explore the development of shorter, less expensive prophylactic regimens more applicable to resource-limited settings. Taking into account that most transmissions occur during delivery and that *in utero* transmission predominantly occurs during the last two months of pregnancy<sup>6</sup> short-course ZDV prophylaxis regimens were designed. Combination ARV regimens were compared with

alternative, less expensive single drugs that could be used in simple regimens. Alternative prophylaxis regimens, like two-dose nevirapine prophylaxis given to mother during labor and to the child immediately after delivery, which had the advantage of being less expensive, ease of administration and effective were implemented in developing countries.

Today, global epidemiology of perinatal HIV depicts two distinct epidemics. Transmission which is reduced to less than 2% in resource-rich countries with implementation of recommendations for universal prenatal HIV counseling and testing, ARV prophylaxis, elective cesarean delivery and avoidance of breastfeeding.<sup>4,5</sup> Transmission rate as low as 0.5% in non-breast-feeding mothers who delivered at term while receiving ARV therapy with a plasma viral load less than 1500 copies/mL has been demonstrated.<sup>5,7,8</sup>

By contrast, the epidemic is strikingly different in resource-limited countries where majority of the HIV-infected women live. In these areas, the three-part, PACTG 076 zidovudine (ZDV) prophylaxis regimen is too complex and expensive for use. Even though effective, less complex and less expensive prophylaxis regimens have now been identified, ARV treatment may not be available to all. Limited maternal-child healthcare infrastructure has difficulty in supporting the addition of HIV counseling and testing and ARV prophylaxis programs; and breastfeeding remains a necessity for most infants. A major challenge is to bridge the gap in prevention of MTCT between resource-rich and resource-limited countries.

## Associated Risk Factors for Mother-to-Child Transmission of HIV (Table 116.1)

In the absence of preventive interventions, published MTCT rates for non-breastfeeding populations in industrialized countries range between 14% and 23%, while the rates in breastfeeding populations in resource-limited settings range between 25% and 48%.<sup>3</sup> With specific interventions in non-breastfeeding populations, the risk of MTCT can be reduced to less than 2%, and to 5% or less in breastfeeding populations.

HIV can be transmitted to the fetus as early as the first and second trimester of pregnancy. However, maternal transmission to the fetus occurs most commonly in the perinatal period. The risk of MTCT of HIV is multi-factorial; maternal plasma HIV RNA levels, mode of delivery and gestational age are independently associated with HIV transmission.<sup>9</sup> The associated risk factors are summarized in Table 116.1.

### IN UTERO TRANSMISSION

Studies have shown that MTCT can occur early in pregnancy, with HIV infection identified in fetuses as early as eight weeks of gestation.<sup>10</sup> HIV can infect the placenta directly and has been detected in fetal autopsy tissue during all three trimesters.<sup>10</sup> The virus is thought to spread cell-to-cell through the placenta, while another possible mechanism involves the passage of maternal mononuclear cells into the fetal circulation.<sup>10</sup> Factors that decrease the placenta's integrity like drug abuse, chorioamnionitis, have also been implicated in *in utero* transmission in the second and third trimester.<sup>10</sup>

### INTRAPARTUM TRANSMISSION

Up to 80% of MTCT is thought to occur during the intrapartum period, defined as the time period during labor and delivery. HIV is detected in cervicovaginal secretions of an infected woman.<sup>11</sup> Contact of infant skin and mucosa with cervicovaginal secretions

or blood or the duration of contact in the maternal genital tract are modifiable risk factors. Breakdown of maternal-fetal barrier followed by maternal-fetal microtransfusions through the placenta, mostly during the first stage of labor is also a proposed mechanism.<sup>12</sup>

Longer duration of rupture of maternal membranes, and thus more fetal contact with cervicovaginal secretions, has been associated with increased MTCT, with 2% increased transmission risk for every additional hour of ruptured membranes.<sup>13</sup> Two individual patient data meta-analyses showed that mode of delivery is not associated with a decreased risk of MTCT after the membrane rupture occurs.<sup>13</sup>

Although there is a large drive to decrease maternal serum viral load with ARV drugs as a means of decreasing MTCT, cervicovaginal HIV viral load and the response to ARV drugs do not always correlate with maternal serum viral load.<sup>11</sup>

### LATE POSTNATAL/BREASTFEEDING TRANSMISSION

Late postnatal breastfeeding transmission is defined as HIV infection in breastfed infants who seroconvert after 4 weeks of age with proof of negative HIV testing prior to 4 weeks of age. A randomized controlled trial in a resource-limited, breastfeeding population which showed that among all infants exposed to breast milk, breastfeeding transmission accounted for approximately 44% of infant HIV infections. The risk of HIV transmission through breast milk is of particular importance as most of the world's HIV-infected women live in areas where formula feeding is not affordable, feasible, available, sustainable, or safe. Increased risk of MTCT correlates with the duration of breastfeeding,<sup>14</sup> higher maternal breast milk viral loads and lower maternal CD4 counts,<sup>15</sup> maternal breast abnormalities such as cracked nipples or breast abscesses<sup>16</sup> and younger maternal age and higher parity.<sup>17</sup>

**Table 116.1:** Associated Risk Factors for Perinatal HIV Transmission

<b>Viral factors</b>	High viral load, Non-syncytium-inducing phenotype, HIV 1 disease
<b>Maternal factors</b>	Advanced disease (low CD4 count, symptoms of AIDS), Primary HIV infection of mother during pregnancy First of twins, Rupture of membranes more than four hours, Maternal bleeding, Mother not on ARV therapy, Vaginal delivery, Other sexually transmitted diseases,
<b>Fetoplacental factors</b>	Chorioamnionitis, Placenta previa, Prematurity (increased peripartum transmission)
<b>Infant factors:</b>	HLA concordance with mother
<b>Postnatal factors:</b>	Breastfeeding  Higher breast milk virus load, Mastitis or maternal nipple lesions, Maternal seroconversion during breastfeeding, Infant having thrush at less than six month age (in breastfeeding infant)

### Recent Guidelines for Prevention of MTCT

- 1. World Health Organization Guidelines (WHO):** ARV drugs for treating pregnant women and preventing HIV infection in infants Recommendations for a public health approach 2010.<sup>18</sup>
- 2. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission:** Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.<sup>19</sup>

### Summary of Various Clinical Trials

Since the success of PACTG 076, various clinical trials have been conducted with the aim of finding more appropriate short, inexpensive treatment protocol. The overall results from these trials suggest that a number of different regimens have similar overall efficacy in preventing *in utero* and intrapartum

transmission, but that the efficacy of such regimens is diminished in breastfeeding populations due to the postnatal acquisition of HIV infection through breast milk. The trials are summarized in Table 116.2.

- A two-part antepartum/infant regimen can effectively reduce the risk of MTCT compared to no prophylaxis.

- A significant proportion of *in utero* transmission appears to occur between 28 and 36 weeks of gestation and is missed when antenatal therapy does not start until 36 weeks of gestation.
- The longer, three-part ZDV regimen is superior in preventing mother to child HIV transmission when it is feasible and affordable to administer such a regimen.

**Table 116.2:** Clinical Trials for Prevention of MTCT

Study	Drugs used during pregnancy	Antenatal and Intrapartum intervention	Postpartum intervention	Mode of infant feeding	Comments
PACTG 076/ANRS 024 trial, USA and France (Connor, 1994) <sup>2</sup>	AZT vs. placebo	Long (from 14 weeks); intravenous IP	Long (six weeks), infant only	Replacement feeding	8.3% in AZT arm vs. 25.5% in placebo arm at 18 months (68% efficacy)
CDC short-course AZT trial, Thailand (Shaffer, 1999) <sup>20</sup>	AZT vs. placebo	Short (from 36 weeks); oral IP	None	Replacement feeding	9.4% in AZT arm vs. 18.9% in placebo arm at 6 months (50% efficacy)
CDC short-course AZT trial, Côte d'Ivoire (Wiktor, 1999; Leroy, 2002) <sup>21</sup>	AZT vs. placebo	Short (from 36 weeks); oral IP	None	Breastfeeding (100%)	16.5% in AZT arm vs. 26.1% in placebo arm at 3 months (37% efficacy) 22.5% in AZT arm vs. 30.2% in placebo arm (26% efficacy) in pooled analysis at 24 months
<b>PETRA trial</b> , South Africa, Tanzania and Uganda (Petra, 2002) <sup>22</sup>	Antenatal, IP/PP AZT + 3TC vs. IP/PP AZT + 3TC vs. IP-only AZT + 3TC vs. placebo	Short (from 36 weeks); oral IP	Short (one week), mother and infant	Breastfeeding (74%, median duration 28 weeks) and replacement feeding	5.7% at six weeks for AP/IP/PP AZT + 3TC, 8.9% for IP/PP AZT + 3TC, 14.2% for IP-only AZT + 3TC and 15.3% for placebo (efficacy compared with placebo: 63%, 42% and 0%, respectively) 14.9% at 18 months for AP/IP/PP AZT + 3TC, 18.1% for IP/PP AZT + 3TC, 20.0% for IP-only AZT + 3TC and 22.2% for placebo (efficacy compared with placebo: 34%, 18% and 0%)
HIVNET 012 trial, Uganda (Jackson 2003) <sup>23</sup>	sd-NVP vs. AZT	Long (from 14 weeks); intravenous IP	Long (six weeks), infant only	Replacement feeding	11.8% in NVP arm vs. 20.0% in AZT arm (42% efficacy) at 6–8 weeks; 15.7% in NVP arm vs. 25.8% in AZT arm (41% efficacy) at 18 months
Perinatal HIV Prevention Trial (PHPT-1), Thailand (Lallemant, 2000) <sup>24</sup>	Four AZT regimens with different durations of AP and infant PP administration, no placebo	Long (from 28 weeks), short (from 36 weeks); oral IP	Long (for 6 weeks), short (for 3 days), infant only	Replacement feeding	Short-short arm stopped at interim analysis (10.5%); MTCT 6.5% in long-long arm vs. 4.7% in long-short arm and 8.6% in the short-long arm at 6 months (no statistical difference) in utero transmission significantly higher with short vs. long maternal therapy regimens (5.1% vs. 1.6%)
Perinatal HIV Prevention Trial (PHPT-2), Thailand (Lallemant, 2004) <sup>25</sup>	AZT alone vs. AZT + maternal and infant sd-NVP vs. AZT + maternal SD NVP	AZT from 28 weeks; oral IP: AZT alone or AZT + SD NVP	AZT for one week with or without SD NVP, infant only	Replacement feeding	AZT-alone arm was stopped due to higher MTCT than the NVP-NVP arm (6.3% vs. 1.1%); in arms in which the mother received SD NVP, MTCT rate did not differ significantly between the infant receiving or not receiving sd-NVP (2.0% vs. 2.8%)
DITRAME Plus (ANRS 1201.0) trial, Abidjan, Côte d'Ivoire (DITRAME 2005) <sup>26</sup>	Open label, AZT + SD NVP	AZT from 36 weeks; oral IP: AZT plus SD NVP	sd-NVP + AZT for one week, infant only	Breastfeeding (54%) and replacement feeding	6.5% (95% CI 3.9–9.1%) at six weeks; historical control group receiving short AZT only had MTCT 12.8% (98% breastfed in historical control group)
DITRAME Plus (ANRS 1201.1) trial, Abidjan, Côte d'Ivoire (DITRAME 2005) <sup>27</sup>	Open label, AZT + 3TC + SD NVP	AZT + 3TC from 32 weeks (stopped at 3 days PP); oral IP: AZT + 3TC + sd-NVP	sd-NVP + AZT for one week, infant only	Breastfeeding (66%) and replacement feeding	4.7% (95% CI 2.4–7.0%) at 6 weeks; historical control group receiving short AZT only had MTCT 12.8% (98% breastfed in historical control group)



Study	Drugs used during pregnancy	Antenatal and Intrapartum intervention	Postpartum intervention	Mode of infant feeding	Comments
Postnatal NVP + AZT trial, Malawi (Taha, 2004) <sup>28</sup>	Neonatal sd-NVP vs. sd-NVP + AZT	No AP ARV; oral IP: SD NVP	sd-NVP with or without AZT for one week, infant only	Breastfeeding (100%)	16.3% in NVP + AZT arm and 14.1% in sd-NVP only arm at 6–8 weeks (difference not statistically significant); MTCT rate at 6–8 weeks among infants who were HIV-uninfected at birth 6.5% and 16.9%, respectively
MASHI, Botswana (Thior, 2006) <sup>29</sup>	Initial: short-course AZT with/without maternal and infant sd-NVP and with/without breastfeeding Revised: short-course AZT + infant sd-NVP with/without maternal sd-NVP and with/without breastfeeding; women with CD4 <200/ $\mu$ L receive HAART	1st randomization AZT from 34 weeks ; oral IP: AZT + either sd-NVP vs. placebo	2nd randomization Breastfeeding + AZT (infant) 6 months + SD NVP, infant only Vs. Formula feeding + AZT (infant) 4 weeks + SD NVP, infant only	Randomization: 50% breastfeeding (median duration 5.8 months), 50% formula feeding	Initial design: In formula feeding arm, MTCT at 1 month 2.4% in maternal and infant sd-NVP arm and 8.3% in placebo arm ( $p = 0.05$ ); in breastfeeding + infant AZT arm, MTCT at 1 month 8.4% in sd-NVP arm and 4.1% in placebo arm (difference not statistically significant) Revised design: MTCT at 1 month 4.3% in maternal + infant sd-NVP arm and 3.7% in maternal placebo + infant sd-NVP arm (no significant difference; no interaction with mode of infant feeding) MTCT at 7 months 9.0% in breastfeeding + AZT arm and 5.6% in formula feeding arm; mortality at 7 months 4.9% breastfeeding + AZT vs. 9.3% formula feeding; HIV-free survival at 18 months 15.1% breastfeeding + AZT vs. 13.9% formula feeding

Abbreviations: AZT, zidovudine; NVP, nevirapine; sd-NVP, single dose nevirapine; IP, intrapartum; AP, antepartum; PP: postpartum.

- Incremental risk of postnatal infections was similar in the ZDV and placebo groups, suggesting that the ZDV benefit, while less in breastfeeding populations, is retained.
- Breast-feeding with extended ZDV prophylaxis was not as effective as formula feeding in preventing postnatal HIV transmission.
- Although HIV transmission was lower in the formula-fed infants, infant mortality at age 7 months was significantly higher in the formula feeding group; the primary causes of death were diarrhea and pneumonia. By age 18 months, HIV-free survival was similar in the two groups.<sup>28</sup>
- Relatively high morbidity and mortality associated with formula feeding in this resource-limited setting, but did not give definitive support to use of extended infant prophylaxis with ZDV to prevent postnatal HIV transmission.
- Alternative prophylaxis regimens, demonstrated that a single-dose intrapartum/newborn nevirapine regimen is superior to an ultra short intrapartum/postpartum ZDV regimen and appears equivalent to the intrapartum/postpartum ZDV/3TC PETRA regimen. Two-dose nevirapine prophylaxis regimen has the advantage of being less expensive, ease of administration, effective and could be implemented in developing countries.
- The latest study “The Kesho Bora study”<sup>30</sup> (a better future in Swahili) was conducted in five sites in Africa, enrolled women with a CD4 count between 200 and 500 cells/ $\mu$ L. The

randomized trial compared the triple-ARV regimen against a control regimen of zidovudine and single-dose nevirapine stopped at delivery as per WHO recommendations 2004. The triple-ARV regimen reduced HIV infections in infants by 43% compared with the control regimen, and reduced the risk of transmission during breastfeeding by more than half. This approach offered new hope for mothers with HIV infection who could not safely feed their babies with infant formula. It is suggested that this would improve the chances of infants remaining healthy and free of HIV infection as breast milk provides optimal nutrition and protects against other fatal childhood diseases such as pneumonia and diarrhea. There is no apparent risk to the health of mothers or their babies associated with the triple-ARV regimen compared with the control regimen. Findings from the Kesho Bora study have strongly influenced the new WHO guidelines on ARVs, prevention of mother-to-child transmission of HIV, and infant feeding.

### Obstetrical Counseling and Management of the HIV-Infected Woman

Care of the HIV-1-infected pregnant woman must involve an ongoing collaboration between the HIV specialist caring for the woman when she is not pregnant, her obstetrician, and the woman herself. The assessment should include evaluation of the following:

- (a) **General counseling related to prevention of perinatal transmission should include information about what is known about risk factors for transmission, particularly those potentially modifiable by the patient.** A long-term treatment plan should be developed with the patient and the importance of adherence to prescribed ARV regimens discussed. Decisions regarding initiation of ARV therapy in women not currently receiving therapy or to continue or alter treatment in women currently receiving therapy should be based on the same criteria as for non-pregnant individuals, with the additional consideration of the potential impact of such therapy on the fetus and infant.
- (b) Clinical assessment and the degree of existing immunodeficiency determined by CD4 cell count and percent. Initiate ART if required for mother's own health.
- (c) HIV-infected pregnant women should be monitored in the same fashion that non-pregnant individuals are monitored; closer monitoring may be warranted in women receiving combination ARV therapy. Measurement of CD4 cell count and HIV RNA levels approximately every trimester (every three to four months).
- (d) Assessment of the need for prophylaxis against *Pneumocystis jiroveci* pneumonia (PCP) or *Mycobacterium avium* complex (MAC), or for treatment of any current HIV-related illnesses. The criteria for initiation of PCP prophylaxis are the same as in non pregnant individuals. Trimethoprim-sulfamethoxazole (TMP/SMX) is the recommended prophylactic regimen. Because of theoretical concerns regarding potential for teratogenicity during the first trimester, aerosolized pentamidine may be considered as an alternative to TMP/SMX during this period due to its lack of systemic absorption.<sup>31</sup>
- (e) The criteria for initiation of chemoprophylaxis for MAC are the same as in non-pregnant individuals. Azithromycin is the drug of choice for prophylaxis of MAC in pregnant HIV-infected women as experience with rifabutin in pregnancy is limited and clarithromycin is teratogenic.
- (f) First trimester ultrasound is recommended for confirmation of gestational age and to guide potential timing of scheduled cesarean delivery if indicated. More intensive monitoring should be considered for the fetus when the mother is taking combination therapy, including assessment of fetal anatomy with ultrasound during the second trimester in women who have received combination ARV drugs in the first trimester (particularly efavirenz), because less is known about the effect of combination therapy on the fetus.
- (g) Screening for maternal syphilis infection as well as other sexually transmitted diseases is not only important in preventing congenital syphilis; one study demonstrated that maternal syphilis infection was associated with an increased risk of MTCT of HIV as well.
- (h) **Elective cesarean section:** Management of HIV-infected pregnant women during labor should focus on minimizing the risk for both perinatal transmission of HIV and

the potential for maternal and neonatal complications. Interventions that prevent infant exposure to infectious maternal blood and secretions in the birth canal during delivery could provide some protection against transmission. Cesarean delivery performed prior to labor would also prevent maternal-fetal microtransfusions that have been shown to occur during uterine contractions. A meta-analysis of 15 prospective cohort studies done to evaluate the relation between elective cesarean section and vertical transmission of human immunodeficiency virus type 1 (HIV-1), showed that of the 8533 mother-child pairs, after adjustment for receipt of ARV therapy, maternal stage of disease, and infant birth weight, the likelihood of vertical transmission of HIV-1 was decreased by approximately 50% with elective cesarean section, as compared with other modes of delivery (adjusted OR, 0.43; 95% CI, 0.33–0.56). The results were similar when the study population was limited to those with rupture of membranes shortly before delivery. The likelihood of transmission was reduced by approximately 87% with both elective cesarean section and receipt of ARV therapy during the prenatal, intrapartum, and neonatal periods, as compared with other modes of delivery and the absence of therapy (adjusted OR, 0.13; 95% CI, 0.09–0.19). Among mother-child pairs receiving ARV therapy during the prenatal, intrapartum, and neonatal periods, rates of vertical transmission were 2.0% among the 196 mothers who underwent elective cesarean section and 7.3% among the 1255 mothers with other modes of delivery.<sup>13</sup> In a review of 1982 patients, who were enrolled from January 1997 through May 2004 after the introduction of HAART, the rates of MTCT fell dramatically from 5% (1997–1998) to 1% (2001–2003). Among the subset of 560 women with undetectable HIV RNA levels, elective cesarean delivery was associated with a significant reduction in transmission risk compared with vaginal delivery or emergency cesarean section on univariate analysis (OR, 0.07; 95% CI 0.02–0.31). However, after adjustment for ARV therapy (none versus any), the effect was no longer statistically significant (adjusted OR 0.52, 95% CI 0.14–2.03,  $p = 0.36$ ).<sup>8</sup>

The American College of Obstetrics and Gynecology (ACOG) recommends that an opinion of elective cesarean delivery should be discussed and recommended for all HIV-infected pregnant women with viral loads above 1000 copies/mL. If the decision is made to perform an elective cesarean delivery, ACOG recommends it be done at 38 weeks gestation, due to the potential risk for labor and membrane rupture before the woman would reach 39 weeks gestation, which is the standard recommended time for operative deliveries in women without HIV infection.<sup>32</sup>

#### INTRAPARTUM PRECAUTIONS

- (a) A thorough review of maternal therapies should be done prior to administration of any drugs during labor to avoid any potentially adverse drug interactions. For example,

midazolam and ergot preparations should be avoided in women receiving protease inhibitors because their metabolism may be delayed by such ARV drugs.<sup>32</sup>

- (b) Because of the potential for increased postoperative maternal morbidity in HIV-infected women undergoing operative delivery, clinicians may opt to administer perioperative antibiotic prophylaxis.
- (c) Whenever possible, intrapartum management of HIV-infected women should minimize invasive procedures that might increase MTCT, such as fetal blood sampling, invasive fetal monitoring with procedures that may cause a break in the infant skin, (e.g., scalp electrodes), and artificial rupture of membranes.
- (d) The duration of membrane rupture is associated with increased risk of MTCT. Thus, in women who are not undergoing elective cesarean delivery, the interval between rupture of membranes and delivery should be minimized through augmenting labor, as needed.
- (e) Other ARV drugs should be continued on schedule during labor or preoperatively to provide maximal virologic effects and to minimize the risk of developing drug resistance.
- (f) Avoidance of episiotomy may decrease exposure of the infant to maternal blood. The infant should be washed before any blood is drawn, injections given, or other invasive procedures performed.

## POSTPARTUM EVALUATIONS

- (a) Maternal medical services during the postpartum period need to be coordinated between obstetric and HIV-specialist healthcare providers.
- (b) Comprehensive care and support services are required for infected women and their families. Comprehensive healthcare services should include HIV-related medical care, psychosocial support, and assistance with family planning and contraception.
- (c) Barrier methods of contraception are recommended to prevent HIV transmission and potential acquisition of HIV superinfection or other sexually transmitted diseases. If hormonal contraception is being considered, potential interaction with ARV and opportunistic infection prophylaxis drugs should be assessed. Several protease inhibitor and non-nucleoside reverse transcriptase inhibitor drugs as well as rifampin and rifabutin may lower hormonal levels and decrease contraceptive efficacy of oral hormones.

## REVISED PMTCT RECOMMENDATIONS

The 2010 revised PMTCT recommendations<sup>18</sup> are based on two key approaches (Fig. 116.1):

1. Lifelong ART for HIV-infected women in need of treatment for their own health, which is also safe and effective in reducing MTCT.
2. ARV prophylaxis to prevent MTCT during pregnancy, delivery, and breastfeeding for HIV-infected women not in need of treatment.

## HIV Infected Pregnant Women in Need for ART for their Own Health (Table 116.3)

The criteria for initiating ART for pregnant women are the same as for non-pregnant women. ART is recommended for all women who have CD4 cell counts of less than or equal to 350 cells/ $\mu$ L, irrespective of WHO clinical staging, and for all women in WHO clinical stage three or four, irrespective of the CD4 cell count. ART irrespective of gestational age should continue throughout pregnancy, delivery, during breastfeeding (if breastfeeding) and thereafter. It should be initiated as soon as the eligibility criteria are met. WHO recommends a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen as first-line ARV treatment regimen for infected individuals who need therapy in resource-limited settings in women, the NNRTI of choice is nevirapine.

The preferred first-line ART regimen in pregnancy comprises of an AZT + 3TC backbone combined with a non-nucleoside reverse transcriptase inhibitor (NNRTI): AZT + 3TC + NVP or AZT + 3TC + EFV. Alternative recommended regimens are TDF + 3TC (or FTC) + NVP and TDF + 3TC (or FTC) + EFV. EFV should not be started in the first trimester, and NVP should be used instead. EFV may be used in the second and third trimesters. The potential for life-threatening hepatic toxicity with chronic NVP therapy in women with CD4 cell counts over 250 cells/ $\mu$ L must also be borne in mind.

Maternal ART should be coupled with the daily administration of NVP or twice-daily AZT to infants from birth or as soon as feasible thereafter until 4–6 weeks of age, irrespective of the mode of feeding.

However, in resource-rich settings, ART is recommended for prevention of mother to child transmission in all pregnant women with HIV RNA levels greater than 1000 copies/mL, and is often used in women with lower RNA levels as well. A protease inhibitor-based HAART regimen can be substituted for prevention of mother to child transmission in women with higher CD4 counts.

## Antiretroviral (ARV) Prophylaxis to Prevent MTCT during Pregnancy, Delivery and Breastfeeding for HIV-Infected Women not in Need of Treatment (Table 116.3)

There are two available options for pregnant women not in need of ART themselves as per the WHO recommendations.

### Option A: AZT prophylaxis starting 14 weeks.

The maternal component of this ARV prophylaxis includes antepartum daily AZT plus single dose nevirapine at onset of labor plus zidovudine and stavudine during labor and delivery and for 7 days postpartum. Early initiation of maternal AZT in pregnancy, that is, starting at 14 weeks in order to further decrease the chance of *in utero* transmission and to limit missed opportunities of starting maternal prophylaxis. Consideration



**Table 116.3:** Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants**1. Antiretroviral therapy for HIV-infected pregnant women who need treatment for their own health****ARV eligibility criteria**

- All women with CD4 of  $\leq 350$  cells/ $\mu$ L, irrespective of clinical staging
- All women with clinical stage 3 or 4, irrespective of CD4 cell count

**When to start ART in pregnant women**

- As soon as feasible

**Recommended first-line regimens for pregnant women**

- AZT + 3TC + NVP or
- AZT + 3TC + EFV or
- TDF + 3TC (or FTC) + NVP
- TDF + 3TC (or FTC) + EFV

**Prophylaxis for infants born to pregnant women on ART**

All infants regardless of infant feeding mode

- NVP or AZT for 4–6 weeks

**2. Antiretroviral prophylaxis for pregnant women who do not need treatment for their own health****When to start ARV prophylaxis**

- As early as 14 weeks of pregnancy

**Prophylaxis regimens for the mother****Option A:**

- AZT during pregnancy plus
- sd-NVP + AZT + 3TC during labor and delivery plus
- AZT + 3TC for 7 days postpartum (may omit sd-NVP and AZT + 3TC if  $> 4$  weeks AZT)

**Option B:**

- AZT + 3TC + LPV/r or
- AZT + 3TC + ABC or
- AZT + 3TC + EFV or
- TDF + 3TC (or FTC) + EFV

Adapted from WHO Guidelines.<sup>18</sup>

can be given to omitting maternal intrapartum and postpartum sd-NVP and AZT + 3TC if the mother has been documented as receiving more than 4 weeks of AZT during pregnancy.

**Option B:** Triple ARV prophylaxis starting from 14 weeks of gestation.

The provision of maternal triple ARV prophylaxis during pregnancy in women who are not eligible for ART results in very low *in utero* and peripartum transmission rates. A high value is also placed on the simplicity of the intervention as it contains only one maternal and one infant regimen and may be available as a once-daily fixed-dose combination. The recommended maternal triple ARV regimens include AZT + 3TC + LPV/r; AZT + 3TC + ABC; AZT + 3TC + EFV; and TDF + 3TC (or FTC) + EFV. NVP-based regimens are not recommended because of the risk of hepatotoxicity for women with high CD4 counts ( $>350$  cells/ $\mu$ L). The same regimen is continued during labor and for 1 week after complete cessation of breastfeeding.

**CLINICAL SCENARIOS**

**HIV positive women in childbearing age group who wish to conceive:** The most important aspect of management involves

counseling. Effective and appropriate contraceptive methods should be provided as part of ART services wherever possible, in order to prevent unintended pregnancy, taking into consideration potential interactions of ARV drugs with hormonal contraceptives that could lower contraceptive efficacy.

Counseling before conception should cover the risk of infant HIV infection, risk factors and PMTCT, potential drug toxicity for mother and infant, safer sexual practices to prevent sexually transmitted infections (STIs), and other general health messages.

It is recommended that there be fully suppressive ART before conception and that it be maintained during pregnancy, labor, delivery and breastfeeding. Preferred ART regimens in such situations should have minimal teratogenic potentials for infants. Women who are planning to become pregnant should use a regimen that does not include EFV, in order to avoid the highest risk period of *in utero* EFV exposure (conception to day 28 of gestation).

**HIV positive women who are pregnant but treatment naïve:**

The first step in this situation is to assess the need of ART for the mother for her own health.

If the mother needs ART for her own health then triple drug therapy is initiated based on same criteria as for non-pregnant women. The primary benefit is the effective reduction in maternal HIV mortality and morbidity, and secondary benefits include the reduction in MTCT and the decrease in infant mortality at 12 months of age.

Recommendations for first-line ART in pregnant women take into account two specific concerns:

Increased NVP hepatotoxicity in women with higher CD4 counts and potential teratogenicity of EFV. While long term use of NVP is not recommended in women with CD4 counts greater than 350 cells/ $\mu$ L, there are conflicting data on whether there is an increased risk of hepatotoxicity with NVP in women with CD4 counts between 250 and 350 cells/ $\mu$ L. In the case of women who require ART for their own health, including pregnant women, it was felt that the benefits of using NVP outweighed the risks of not initiating ART. Close clinical monitoring (and laboratory monitoring, if feasible) during the first 12 weeks of therapy is recommended when NVP is initiated in women with a CD4 cell count of 250 to 350 cells/ $\mu$ L.

EFV should not be initiated in the first trimester of pregnancy but may be initiated in the second and third trimesters. There is low quality evidence of the risks of EFV causing neural tube defects. The rates of overall birth defects reported in association with EFV, NVP, LPV/r or TDF appear similar and are consistent with rates reported in congenital defects registries in general populations.

**HIV positive women who become pregnant while receiving ART:**

For women planning a pregnancy or who become pregnant while receiving ART, some additional considerations mainly include the choice of regimen based on gestational age, the clinical and laboratory findings, and the risk of MTCT. Known benefits and potential risks of ARV use during pregnancy (particularly during the first trimester) should be discussed with all women.

The interruption of treatment among eligible women receiving ART for their own health who have a good immune response to ART has been associated with viral rebound and renewed CD4 cell decline, increasing the risk of MTCT and HIV disease progression.<sup>33,34</sup> Discontinuing treatment before or during pregnancy is therefore not recommended.

For women receiving an EFV-based regimen and who plan to become pregnant, substitution of NVP in the place of EFV for at least the periconception period is recommended. Alternatively, a triple NRTI or PI-based regimen can be given. Some concerns exist about exposure to TDF *in utero* and the risks of abnormal fetal bone development. However, for women requiring ART and receiving TDF who become pregnant, the benefits of continuing treatment are likely to outweigh the theoretical risks of toxicity for the infant.

**HIV positive women on treatment and have had prior exposure to antiretrovirals for PMTCT:** Resistance to NNRTI drugs is an important concern for PMTCT regimens. The long half-life of NVP and its low genetic barrier to resistance means that detectable drug levels persist for 2–3 weeks in the presence of active viral replication following a single maternal dose.<sup>35–37</sup> EFV also has a long half-life, with detectable drug levels for more than 21 days following discontinuation.<sup>38</sup> This has clinical relevance in pregnancy where ARV drugs may be provided solely for prophylaxis against perinatal transmission and discontinued after delivery or after breastfeeding.

In a meta-analysis of 10 studies, the prevalence of NVP resistance in women 4–8 weeks following sd-NVP was 35.7%.<sup>39</sup> Additionally, NNRTI resistance can develop in women receiving NNRTI-based triple drug prophylaxis regimens following discontinuation of prophylaxis, particularly if all drugs are stopped simultaneously.<sup>40</sup> In most women, resistant virus can no longer be detected 6–12 months after exposure. However, low levels of viral resistance can persist for longer periods and in some cases can remain present in latently infected cells.<sup>41–43</sup>

Data suggest that women starting NNRTI-based ART within 6–24 months of sd-NVP exposure have higher rates of viral failure than those without sd-NVP exposure. A definite relationship between time from sd-NVP exposure to starting NNRTI-based ART has been observed but has varied between studies, with a significant improvement in response if there were more than 12 months between sd-NVP exposure and start of therapy.<sup>44–51</sup> A tail regimen for a minimum of 7 days is recommended following sd-NVP or cessation of NNRTI-based triple prophylaxis. The tail regimen is provided in order to suppress virus and prevent persistent single drug NNRTI exposure. Much lower NNRTI resistance rates of 0–7% at 2–6 weeks postpartum have been reported with the use of various tail regimens.<sup>52–57</sup>

The choice of ART regimen for pregnant women who require treatment for their own health but who have had exposure to ARV drugs for PMTCT prophylaxis in earlier pregnancies will therefore depend on the time since ARV PMTCT drug exposure at the time ART is being initiated, and whether a tail regimen was used for prevention of resistance following exposure to sd-NVP (given alone or in combination with other ARVs). As discussed

in the revised 2010 guidelines, ARV therapy for HIV infection in adults and adolescents,<sup>18</sup> viral load testing, if available, is particularly useful for monitoring response to treatment in this special situation.

A non-NNRTI-based ART regimen (e.g., a LPV/r-based regimen) is recommended for women who require ART for their own health who have received, within 12 months of initiating treatment, sd-NVP alone or in combination with other drugs without an NRTI tail. If a non-NNRTI-based regimen is not available, an NNRTI-based regimen may be started, but it is recommended that viral load testing (if available) be performed after 6 months of ART and, if the viral load is greater than 5000 copies/mL a switch to a boosted PI regimen (e.g., LPV/r) is recommended.

For women who have received sd-NVP alone or in combination with other drugs with a tail within 12 months of starting treatment, the initiation of a standard NNRTI-based ART regimen is recommended. Viral load testing (if available) is recommended after 6 months of ART and, if the viral load is greater than 5000 copies/mL a switch to a boosted PI regimen (e.g., LPV/r) is recommended.

For women who have received sd-NVP (alone or in combination with other drugs) more than 12 months before starting treatment (with or without a tail), a standard NNRTI-based ART regimen is recommended. As in the other scenarios above, if available, the viral load should be evaluated after 6 months of ART, and if greater than 5000 copies/mL a switch to a boosted PI regimen (e.g., LPV/r) is recommended.

In our own center, among 60 treatment-naïve HIV-1-infected patients, mutations were screened at codons 70 and 215 (conferring resistance to zidovudine) and at codon 184 (conferring resistance to lamivudine). Most of the patients showed a mixture of both wild-type and mutant virus. Mutant variants were observed in many patients, especially at codon 70 (48 patients [80%]) and codon 184 (19 patients [31.67%]). In contrast, the frequency of mutation at codon 215 was found to be very low (1 patient [1.67%]).<sup>58</sup> Thus, with increasing use of ARV drugs and previous exposure, individual tailoring of ART regimens may be required.

## Neonatal Monitoring

- A complete differential blood count should be performed as a baseline evaluation prior to administration of ZDV.
- Infants who have anemia at birth or who are premature warrant more intensive monitoring.
- Following completion of the ZDV prophylaxis regimen, all infants born to HIV-infected women should be placed on PCP prophylaxis at 6 weeks of age, unless there is adequate virologic test information to presumptively exclude HIV-1 infection. The preferred regimen is trimethoprim 150 mg/m<sup>2</sup>/day with sulfamethoxazole 750 mg/m<sup>2</sup>/day in divided doses two times a day and given three times per week on consecutive days. Prophylaxis is continued until at least age 12 months in all infants diagnosed as infected or whose infection status is not yet determined. After age 12

months, prophylaxis is continued only in infected children, depending upon their CD4 cell count. Prophylaxis is not recommended for infants who meet criteria for presumptive or definitive lack of evidence of HIV-1 infection.

## Non-antiretroviral Interventions to Reduce Perinatal HIV Transmission

A number of interventions to prevent perinatal HIV transmission that does not involve ARV drugs have been evaluated in the developing world. These include the following:

**Treatment/prophylaxis of malaria and sexually transmitted diseases:** Placental malaria was associated with increased risk of MTCT of HIV infection after adjustment for viral load in various studies.<sup>59</sup> There have not been any randomized trials to evaluate malaria chemoprophylaxis during pregnancy as a preventive strategy to reduce perinatal transmission in malaria-endemic locales. Given the availability of effective short-course ARV prophylaxis to reduce transmission, it is likely this question will need to be addressed through careful cohort studies.

Some studies have suggested that sexually transmitted diseases (e.g., gonorrhea, herpes simplex virus infection) may facilitate perinatal HIV transmission. Treatment of sexually transmitted infections might provide an effective intervention to decrease both sexual and perinatal HIV transmission.<sup>60,61</sup>

**Nutritional supplementation:** Multivitamin supplementation, but not vitamin A supplementation alone, was associated with significant improvement in non-HIV related pregnancy outcomes including fetal death (5.9 vs. 9.6% in the multivitamin versus placebo groups, respectively), low birth weight (8.8 vs. 15.8%), severe preterm birth at younger than 34 weeks (6.2 vs. 10.2%), and small for gestational age infants (10 vs. 17.6%) in a randomized controlled trial of 1075 pregnant women who, at 12–27 weeks of gestation, were assigned to placebo, vitamin A alone, multivitamins excluding vitamin A, or multivitamins including vitamin A; one-third were vitamin A deficient at baseline.<sup>62</sup>

**Vaginal virucidal cleansing:** While use of vaginal virucides does not appear to reduce perinatal HIV transmission, vaginal virucidal cleansing, like vitamin supplementation, is inexpensive, easily administered, does not require HIV testing for implementation, and is of potential overall benefit to infected and uninfected women

**Prophylaxis of chorioamnionitis:** Chorioamnionitis is associated with significant inflammation and activation of immune cells in the placenta, which could lead to breaks in the placental barrier, allowing passage of virus or infected lymphocytes from the mother to the fetus. However, data from a controlled clinical trial in Malawi and Zambia in which empiric therapy for chorioamnionitis with a short course of antibiotics was given to infected pregnant at 20–24 weeks gestation and again during delivery found that such therapy did not reduce perinatal HIV transmission or infant morbidity and mortality.<sup>63</sup>

**Breastfeeding and HIV infection:** Mother-to-child HIV transmission occurs *in utero*, peripartum, and postnatally via

breastfeeding; the risk of HIV transmission to the infant can be significantly reduced with ARV medications. Research on breast milk transmission is particularly critical since there are now effective short-course ARV prophylaxis regimens that can decrease *in utero* and intrapartum HIV transmission. In many resource-limited settings, replacement infant feeding is not safe, affordable, sustainable or culturally acceptable, and breastfeeding is the norm even among HIV-infected women.

- (a) Replacement feeding is recommended for infants born to HIV-infected mothers in the United States, which is the current standard of care in resource-rich settings. However, in developing countries, replacement feeding may be associated with greater infant morbidity and mortality from diarrheal disease, pneumonia, and other infectious diseases.
- (b) The risk of HIV transmission through breast milk is greatest in the first several months of life; however, a lower but constant risk persists throughout the entire breastfeeding period.
- (c) The risk of infant transmission increases with increased levels of maternal HIV RNA in plasma or breast milk.
- (d) ARV medications significantly decrease the risk of mother-to-child transmission of HIV during the antepartum, intrapartum, and early postpartum periods. However, an excess risk of HIV transmission occurs if ARV medications are discontinued during the breastfeeding period.
- (e) For HIV-infected mothers in resource-limited settings who are breastfeeding, postnatal ARV medications for the mother or infant during the breastfeeding period, rather than no drug intervention is recommended. The preferred interventional strategy will depend on the mother's CD4 cell count and HIV clinical status.
- (f) Among HIV-infected women with a CD4 cell count less than 350 cells/ $\mu$ L or with WHO stage 3 or 4 disease, antenatal combination ARV therapy should be started as soon as feasible, regardless of gestational age and continued for the lifetime of the woman. This strategy leads to decreased risk of maternal morbidity and mortality and a decreased risk of HIV transmission to the infant during breastfeeding.
- (g) For women with a CD4 cell count greater than 350 cells/ $\mu$ L and WHO stage 1 or 2 disease, either neonatal or maternal prophylaxis is a viable option to prevent infant HIV transmission. Both interventions should be continued during the entire period of breastfeeding and for one week beyond discontinuation. Standard ARV prophylaxis also needs to be offered for the prevention of mother-to-child transmission of HIV during the antepartum, intrapartum, and early postpartum periods.

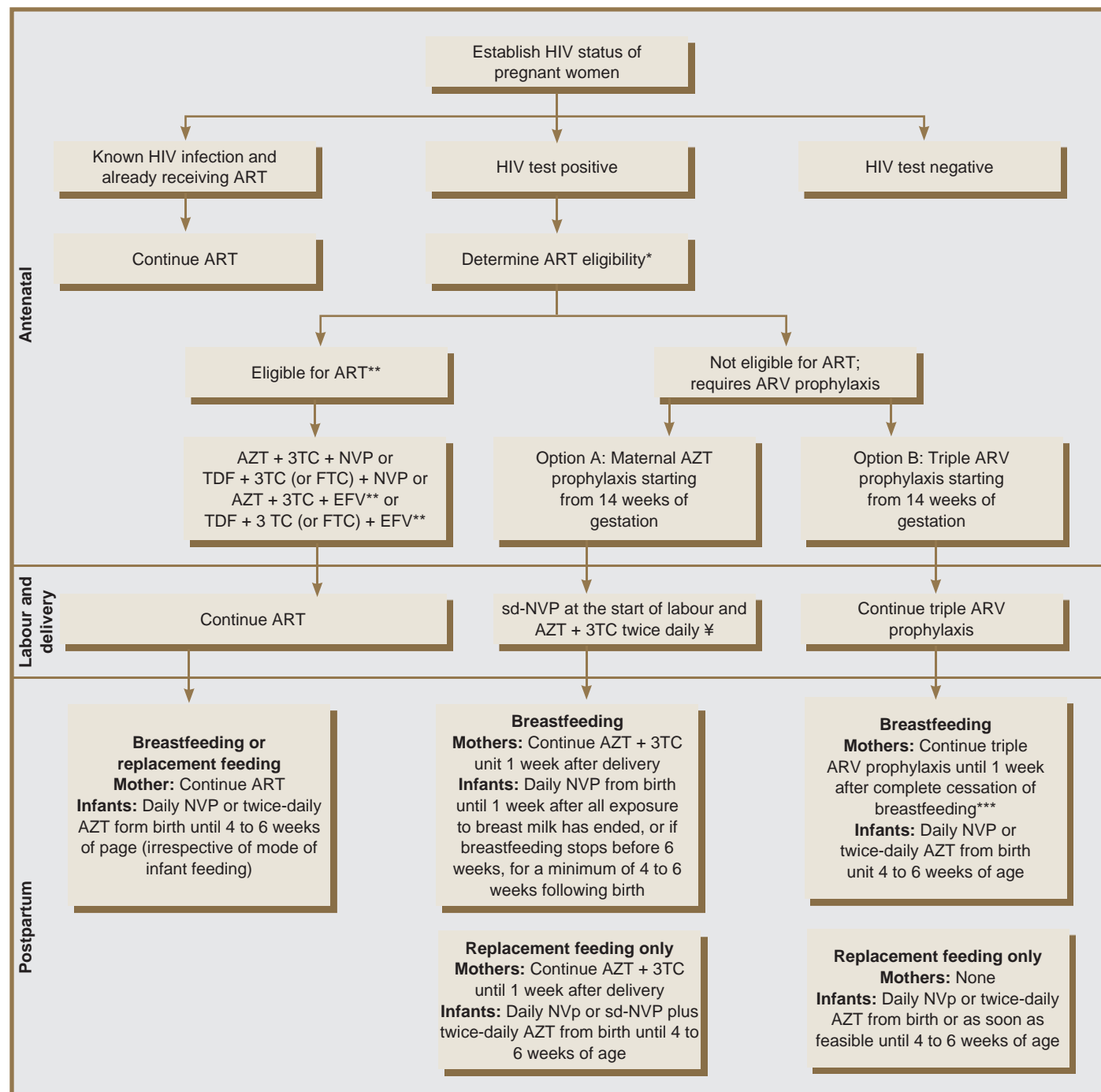
Exclusive breastfeeding, in combination with maternal or infant ART, is recommended for the first six months of life as it leads to nutritional and immunologic benefits for the infant. WHO recommends that national authorities should decide whether health services would principally counsel mothers to



either breastfeed and receive ARV interventions or avoid all breastfeeding, as the strategy that would most likely give infants the greatest chance of HIV-free survival. Where breastfeeding is judged to be the best option, exclusive breastfeeding for the first 6 months followed by introduction of appropriate complementary food thereafter must be emphasized. Breastfeeding may be continued for 12 months and gradually weaned within 1 month.

The postpartum guidelines of ARV drugs to be initiated along with breastfeeding are as summarized (Fig. 116.1).

In our own experience, most parents opt for replacement feeding than breastfeeding. With appropriate counseling and support, mothers are able to provide formula or cow's milk with spoon in a hygienic manner. The diarrheal infections noted are negligible. The clean hand practices, sterilization of utensils,



\*Start ARV prophylaxis while waiting to determine ART eligibility.

\*\*Avoid use of EFV in first trimester; use NVP instead.

\*\*\*When stopping any NNRTI-based regimen, stop the NNRTI first and continue the two NRTIs for 7 days and then stop them to reduce the chance of NNRTI resistance.

‡ If AZT was taken for at least the last 4 weeks before delivery, omission of the maternal sd-NVP and accompanying tail (AZT + 3TC) can be considered.

Fig. 116.1: Flowchart depicting the WHO recommendations for prevention of mother-to-child transmission.

boiling of milk need to be periodically emphasized during their routine as well as immunization visits.

## Indian Scenario<sup>1,64</sup>

The Prevention of Parent to Child Transmission of HIV/AIDS (PPTCT) program was started in the country in the year 2002 following a feasibility study in 11 major hospitals in the five high HIV prevalence states. Currently, there are more than 4000 Integrated Counseling and Testing Centers (ICTCs) in the country, most of these in government hospitals, which offer PPTCT services to pregnant women. Of these ICTCs, 502 are located in Obstetrics and Gynecology Departments and in Maternity Homes where the patient load predominantly comprises of pregnant women.

The Joint Technical Mission on PPTCT (2006) estimated that of 27 million annual pregnancies in India, 189,000 occur in HIV infected pregnant women. In the absence of any intervention, an estimated cohort of 56,700 infected babies will be born annually. The PPTCT programmed aims to prevent the perinatal transmission of HIV from an HIV infected pregnant mother to her newborn baby. The programmed entails counseling and testing of pregnant women in the ICTCs. Pregnant women who are found to have HIV infection are given a single dose of nevirapine at the time of labor; their newborn babies also get a single dose of nevirapine immediately after birth so as to prevent transmission of HIV from mother to child.

## Conclusions

International clinical trials have identified effective, simple, and less expensive ARV prophylaxis regimens more relevant to resource-limited countries. However, the availability of an effective intervention is only one of the several requirements for prevention of MTCT.

In order to access ARV prophylaxis, adequate systems of antenatal care are needed; however, on a global basis, one third of women lack prenatal care. Additionally, prenatal HIV counseling and testing are needed to identify HIV-infected women who could be offered effective prophylaxis. Yet, these services are not available in many resource-poor countries, and the cost of such programs has significantly contributed to the slow implementation of mother to child HIV transmission prevention programs. Additionally, in many resource-poor settings, postnatal transmission of HIV through breastfeeding remains a significant problem due to the lack of safe infant feeding alternatives.

It is increasingly recognized that programs to reduce mother to child HIV transmission must also consider the health of the mother. ARV prophylaxis regimens, while preventing HIV transmission to the infant, do not prevent progression of HIV disease and death in the mother. Studies have shown increased mortality in children whose mothers have died of HIV infection, even if the child is uninfected.

Additionally, provision of ARV therapy for HIV-infected individuals may be the most effective inducement for HIV

testing and decreasing the stigma of HIV, and hence increasing acceptance of prenatal testing by woman. The gap between the resource rich countries with negligible transmission with optimal antenatal care, HAART and replacement feeding and the developing countries needs to be bridged to have a generation of children free from AIDS.

### Summary

Perinatal transmission is the most important route of human immunodeficiency virus (HIV) infection in children. Significant reduction in the risk of perinatal transmission is possible with implementation of recommendations for universal prenatal HIV counseling and testing, and appropriate antiretroviral prophylaxis regimens. The first step is assessing the mother's need for antiretroviral therapy for her health, based on same criteria as for non-pregnant women. Triple-drug ART is recommended for all women who have CD4 cell counts of  $\leq 350$  cells/ $\mu$ L, irrespective of WHO clinical staging, and for all women in WHO clinical stage 3 or 4, irrespective of the CD4 cell count. ART irrespective of gestational age should continue throughout pregnancy, delivery, during breastfeeding (if breastfeeding) and thereafter. EFV should not be used in the first trimester due to potential teratogenicity. Prophylaxis regimens are recommended for mothers who do not need ART for their own health. These include AZT prophylaxis starting 14 weeks, sd-NVP + AZT + 3TC during labor and delivery plus AZT + 3TC for 7 days postpartum or triple ARV prophylaxis starting from 14 weeks of gestation. Triple-drug regimen is continued during labor and for 1 week after complete cessation of breastfeeding. Replacement feeding is recommended for infants born to HIV-infected mothers in the United States, which is the current standard of care in resource-rich settings. However, in developing countries, replacement feeding may be associated with greater infant morbidity and mortality from diarrheal disease, pneumonia, and other infectious diseases. For HIV-infected mothers in resource-limited settings who are breastfeeding, postnatal antiretroviral medications for the mother or infant during the breastfeeding period, rather than no drug intervention, is recommended.

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# Guidelines for the Management of HIV-Associated Opportunistic Infections

Phillip J. Read

# 117

## Introduction

Opportunistic infections (OIs) represent an important cause of mortality and morbidity for those infected with HIV. Antiretroviral therapy (ART) as well as the judicious use of primary chemoprophylaxis, when available, has resulted in a large reduction in HIV-related deaths, and estimates of prognosis of people with HIV infection approach that of the non-infected population. However, access to ART is not universal, and not all HIV infected individuals taking treatment achieve immune reconstitution. These factors, combined with the problem of late-presentation of people with undiagnosed HIV means that clinicians are likely to be confronted by patients with HIV-associated OIs for many years to come.

There are several reference guidelines available to assist the clinician in the management of OIs. The specific presentations and diagnostic tools required to confirm or refute these diagnoses are too extensive to cover in this chapter, and readers are advised to refer to the relevant chapter in this book, or to review the full guidelines online.

This chapter provides information on the treatment of common OIs summarized from three highly regarded sources; the Centers for Disease Control and Prevention,<sup>1</sup> USA, the World Health Organisation (South East Asian Office),<sup>2</sup> and the Indian National AIDS Control Organisation/Ministry of Health & Family Welfare, India.<sup>3</sup> The website addresses for these guidelines are given in the reference section of this chapter. The availability and cost for each treatment will vary from country to country, so where possible the guidelines are compared, and preferred and alternative therapies listed to offer the broadest range of options to those working in resource-rich and resource-limited settings. Where available, information on the likely response to therapy and secondary prophylaxis is given, as well as key side-effects.

The question of when to commence ART after diagnosis and treatment of an OI is not fully resolved. A balance between triggering Immune Reconstitution Inflammatory Syndrome (IRIS) and the overlapping toxicities of several OI treatment regimens with ART must be balanced against the risk of further

HIV disease progression.<sup>4</sup> At this stage it is likely that the benefit of early initiation (within 2 weeks) of ART will depend not only on the specific OI, but also on the availability of resources to manage the complications of co-administration.

## Viral Opportunistic Infections

### CYTOMEGALOVIRUS (TABLE 117.1)

Prior to the advent of ART, cytomegalovirus retinitis was the most common ophthalmic OI, with a prevalence of around 30% in those with a CD4 count less than 50 cells/ $\mu$ L. Similarly, it may also cause colitis, esophagitis, encephalitis, and occasionally a pneumonitis.

### VARICELLA ZOSTER VIRUS (TABLE 117.2)

Although not necessarily AIDS-defining, varicella (herpes) zoster reactivation is 15–20 times more common in HIV positive individuals compared to the general population. It typically presents as a cutaneous disease, which may be multidermatomal, but may also cause retinal necrosis or encephalitis. Previously unexposed patients may be at risk of disseminated chicken pox.

### HERPES SIMPLEX VIRUS (TABLE 117.3)

Herpes simplex virus (HSV) infection of the oral or genital mucosa is extremely common in HIV positive individuals. Mild primary or recurrent episodes of herpes labialis or herpes genitalis can be managed similarly to the HIV negative population (see HSV management guidelines chapter). Suppressive HSV therapy may be required at either standard or increased dosage. The recommendations in the table below apply to severe mucocutaneous or visceral disease, and HSV encephalitis.

### HUMAN HERPES VIRUS-8 (KAPOSI SARCOMA HERPES VIRUS) (TABLE 117.4)

Kaposi sarcoma (KS) is the commonest AIDS-defining malignancy. Disease severity can be assessed using the T (extent of tumor) I (Immune status) S (severity of systemic illness) score. A good

**Table 117.1:** Recommendations for the Management of Cytomegalovirus Infection

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
<p><b>Preferred: Retinitis</b> If sight-threatening— Ganciclovir intraocular implant + valganciclovir 900 mg PO 2 × daily for 2–3 weeks induction, then 900 mg PO 1 × daily until immune restoration Consider single dose intravitreal ganciclovir if implant likely to be delayed If peripheral lesions only— Valganciclovir 900 mg PO twice daily for 2–3 weeks followed by 900 mg once daily until immune restoration</p> <p><b>Alternative: Retinitis</b> Ganciclovir 5 mg/kg IV 2 × daily for 2–3 weeks followed by either ganciclovir 5 mg/kg IV daily or valganciclovir 900 mg PO daily Or Foscarnet 180 mg/kg IV in 2–3 divided doses for 2–3 weeks then 90–120 mg/kg IV daily Or Cidofovir 5 mg/kg IV weekly for 2 weeks, then 5 mg/kg every other week with saline hydration pre- and post treatment. Give probenecid 2 g PO 3 hours before therapy, and two further 1 g doses at 2 and 8 hours after therapy</p> <p><b>Preferred: Esophagitis, colitis, or pneumonitis</b> Ganciclovir IV or Foscarnet IV dosed as above for 21–28 days or until clinical resolution Or Valganciclovir 900 mg 2 × daily PO if absorption adequate</p> <p><b>Preferred: Neurological disease</b> Consider combination of ganciclovir IV and foscarnet IV followed by valganciclovir PO plus foscarnet IV until immune restoration</p>	<p>No specific guidance. Treat if drugs available. If not, commence ART</p>	<p><b>Preferred: All forms of disease</b> Ganciclovir 5 mg/kg IV 2 × daily for 2–3 weeks followed by oral ganciclovir capsules 1 g 3 × daily or ganciclovir IV once daily 5–7 days/week or valganciclovir 900 mg daily or Foscarnet IV 60 mg/kg 3 × daily or 90 mg/kg 2 × daily IV daily for 2–3 weeks then once daily maintenance Or Cidofovir IV weekly for 2 weeks with probenecid</p> <p><b>Alternative: Retinitis</b> Intravitreal injections: Ganciclovir 0.1 ml intravitreal injection at a dose of 200–4000 µg 3 × weekly for 2–3 weeks induction followed by weekly maintenance Or Foscarnet 1.2–2.4 mg twice weekly for 2–3 weeks followed by 1.2 mg weekly Or Cidofovir 20 µg weekly</p>

Intravitreal cidofovir not included in CDC guidelines due to risk of iritis, ocular hypotony and visual impairment.

Ganciclovir and valganciclovir may cause hematological abnormalities, in particular neutropenia.

Foscarnet and cidofovir are associated with renal and electrolyte disturbance.

CMV is a potential cause of IRIS, and close monitoring of retinal lesions after the institution of ART is recommended.

prognosis is possible if lesions are cutaneous only, if the CD4 count is more than 150 cells/µL and the absence of “B” symptoms. There may a dramatic response to ART, but cases of IRIS have also been described. Systemic therapy as an adjunct to ART is recommended where possible if there are greater than 25 cutaneous lesions, visceral involvement or edema, a failure to respond to other treatments or significant “B” symptoms. Adjunct treatment is rarely curative, and remission requires immune reconstitution.

**Human herpes virus-8** is also implicated in the etiology of primary effusion (body cavity) lymphoma and in multicentric Castleman disease.

The role of HHV-8 viral load monitoring in assessing response to therapy in HHV-8 related disease is an area of expanding research.

### JC VIRUS (PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY [PML]) (TABLE 117.5)

JC virus has been identified as the cause of PML, a condition with a poor prognosis even in the era of effective ART. Brain biopsy, although rarely necessary, provides a definitive diagnosis, but CSF examination may be positive for JC virus in 75–80% of cases, and MRI or CT scan of the head may show white matter disease. Diagnosis in the absence of these tests is usually clinical.

ART may be associated with improvement, but an inflammatory syndrome and worsening consequent to ART has also been described.



**Table 117.2:** Recommendations for the Management of Varicella Zoster Infection

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
<b>Preferred:</b> Treat within 1 week of rash Aciclovir 20 mg/kg up to 800 mg PO 5 × daily Or Valacyclovir 1 g PO 3 × daily Or Famciclovir 500 mg PO 3 × daily Duration: 5–7 days for varicella, and 7–10 days if shingles If severe or complicated varicella or extensive shingles: initiate with aciclovir 10–15 mg/kg IV 3 × daily for 7–10 days, switch to oral therapy to complete a 10–14 days course <b>Alternative:</b> Foscarnet 90 mg/kg IV 2 × daily if aciclovir resistance <b>Acute retinal necrosis:</b> Aciclovir 10 mg/kg IV 3 × daily for 10–14 days followed by valacyclovir 1 g PO 3 × daily for 6 weeks	<b>Preferred:</b> Local lesion care with gentian violet and chlorhexidine Treat if within 72 hours of rash Aciclovir 800 mg PO 5 × daily for 7 days. Consider famciclovir or valacyclovir if available Add aciclovir ointment every 4 hours topically if ophthalmic involvement.	<b>Preferred:</b> Treat within 3 days of rash Aciclovir 20 mg/kg PO up to maximum dose of 800 mg 4–5 × daily If extensive disease or visceral involvement, use acyclovir 10 mg/kg IV 3 × daily for 7–10 days until lesions and fever resolve. Consider switch to oral valacyclovir or famciclovir if no fever or visceral involvement Topical methylene blue or millian may combat superinfection

In addition to simple analgesics, pain relief may require gabapentin, amitriptyline, or opioids.

High-dose intravenous acyclovir may cause crystal nephropathy and renal impairment.

Antiviral therapy reduces the duration of lesions, and subsequent pain if started soon after symptoms.

**Table 117.3:** Recommendations for the Management of Herpes Simplex Infections

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
<b>Preferred:</b> Severe mucocutaneous infections— Initial therapy aciclovir 5 mg/kg IV 3 × daily Change to PO therapy after lesions regress <b>Preferred:</b> Aciclovir-resistant mucocutaneous infections— Foscarnet 80–120 mg/kg/day IV in 2–3 divided doses until clinical response <b>Preferred:</b> HSV encephalitis— Aciclovir 10 mg/kg IV q8h for 21 days	<b>Preferred:</b> Usually self-limiting and may not require treatment Care of the local lesion: Burow solution or gentian violet or chlorhexidine for 15 minutes 4–5 times/day plus aciclovir 200–400 mg 5 times daily for 7 days if available	<b>Preferred:</b> Aciclovir 400 mg 3 × daily for 7–14 days if disseminated mucocutaneous disease In severe infection or encephalitis: Aciclovir 5 mg/kg IV 3 × daily for 10 days

High-dose intravenous aciclovir may cause crystal nephropathy and renal impairment.

Topical cidofovir or trifluridine may be effective in aciclovir-resistant HSV.

Secondary prophylaxis post encephalitis may be useful.

Control of HSV ulceration may be important in HIV control.

HSV suppression has a very modest effect in reducing HIV viral load.

**Table 117.4:** Recommendations for the Management of Human Herpes Virus-8 (HHV-8)

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
<b>Preferred:</b> Initiate or optimize ART For visceral, disseminated cutaneous KS or primary effusion lymphoma, chemotherapy plus ART should be used Consider valganciclovir or ganciclovir as adjunct therapy For Multicentric Castleman disease: <b>Preferred:</b> Valganciclovir 900 mg PO 2 × daily or ganciclovir 5 mg/kg IV 2 × daily <b>Alternative:</b> Rituximab 375 mg/m <sup>2</sup> for 4–8 weeks	No specific recommendation. Start ART.	<b>Preferred for KS:</b> commence ART For facial local lesions consider: Liquid nitrogen cryotherapy Or Intralesional vinblastine Or Alpha-interferon Or Excision Consider adjunct therapy with Ganciclovir or Foscarnet or Cidofovir (no dose recommendations given)

For toxicities of ganciclovir, foscarnet, and cidofovir see Table 117.1.

Evidence for anti-herpes medications in this setting is lacking.

**Table 117.5:** Recommendations for the Management of PML

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
<b>Preferred:</b> No specific treatment targeting JCV proven, initiate ART If worsening seen with ART and imaging suggests inflammatory component, consider corticosteroids	No specific recommendation	Commence ART

Although potentially active against JCV *in vitro*, antiviral medications such as cidofovir or ganciclovir have proven disappointing in clinical studies.

## Fungal Opportunistic Infections

### PNEUMOCYSTIS PNEUMONIA (TABLE 117.6)

Pneumocystis pneumonia (PCP) is caused by the fungus *Pneumocystis jirovecii*, an environmental organism. It is one of the most common OIs, and prior to ART affected over half of HIV-positive individuals at some point. Primary and secondary prophylaxis are important in disease prevention. Primary prophylaxis should be instituted in anyone with a CD4 count of less than 200 cells/ $\mu$ L, a CD4 percentage of less than 14%, or other AIDS conditions or signs of immunosuppression (such as persistent oral candidiasis). Early initiation of ART within the first two weeks has been shown to improve outcome.<sup>4</sup>

Cotrimoxazole (trimethoprim-sulfamethoxazole) commonly causes adverse event such as rash, fever and nausea. However it is

often possible to treat through these reactions using symptomatic management and careful observation of liver function.

### CANDIDIASIS (TABLE 117.7)

Candida species are common commensal organisms in immunocompetent and immunodeficient populations. Candida most frequently causes mucosal disease. Oropharyngeal or esophageal candidiasis represents likely progression of disease, but genital candidiasis is common at all CD4 strata. Most candida is of the *C. albicans* species, but other species such as *C. glabrata* or *C. tropicalis* may also be present, which may be less susceptible to topical azoles or oral fluconazole. Fluconazole-resistant *C. albicans* has also been described in patients on long-term suppressive therapy with recalcitrant disease. Disseminated candidiasis is relatively rare and not covered in this guideline, but may be

**Table 117.6:** Recommendations for the Management of PCP

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
<b>Preferred:</b> Trimethoprim-sulfamethoxazole 90–120 mg/kg/day in 3–4 divided doses for 21 days Intravenous if severe Oral if mild-moderate  <b>Alternative: Severe</b> Pentamidine 4 mg/kg IV once daily Or Primaquine 15–30 mg PO once daily plus clindamycin 600–900 mg IV q6-8h or clindamycin 300–450 mg PO q6-8h  <b>Alternative: Mild-moderate</b> Primaquine 15–30 mg PO once daily plus clindamycin 300–450 mg PO q6-8h Or dapsone 100 mg PO once daily plus trimethoprim 15 mg/kg/day in 3 divided doses Or Atovaquone 750 mg PO bid  <b>If PaO<sub>2</sub> &lt;70 mmHg on room air or Alveolar – arterial O<sub>2</sub> gradient (A-a gradient) &gt;35 mmHg</b> Prednisolone 40 mg PO bid day 1–5 40 mg PO once daily days 6–10 20 mg once daily days 11–21	<b>Preferred:</b> Trimethoprim-sulfamethoxazole 100 mg/kg/daily in 4 divided doses for 21 days. Intravenous if severe until well enough for oral.  <b>Oral dose:</b> 2 × 480 mg tablets 4 × daily if <40 kg 3 × 480 mg tablets 4 × daily if >40 kg  <b>Alternative:</b> Clindamycin 450 mg (oral) or 600 mg (IV) 3 × daily plus primaquine 15 mg PO once daily for 21 days  <b>If severe:</b> Prednisolone 20 mg 4 × daily with reducing dose of 7–10 days depending on response	<b>Preferred:</b> Trimethoprim-sulfamethoxazole 90–120 mg/kg/day in 3–4 divided doses for 21 days  <b>Oral dose:</b> 2 × Co-trimoxazole 960 mg tablets 3 × daily  <b>Alternative:</b> Trimethoprim 15 mg/kg/day PO plus dapsone 100mg daily Or Pentamidine 4 mg/kg IV once daily Or Clindamycin 600–900 mg IV q6-8h or 300–450 mg PO q6h plus primaquine 15–30 mg Or Atovaquone 750 mg bid PO  <b>If severe disease (PaO<sub>2</sub> &lt;70 mmHg or A-a gradient &gt;35 mmHg):</b> Prednisolone 40 mg bid for 5 days 40 mg once daily for 5 days 20 mg once daily until completion of treatment

All guidelines suggest steroids should be administered as soon as indicated, and certainly within the 1st 72 hours.

Improvement may not be noted for 3–5 days in some individuals and earlier treatment changes are not advised unless for toxicity.

Duration of therapy is recommended as 21 days for all regimens.

Secondary prophylaxis should follow treatment until immune restoration.

**Table 117.7:** Recommendations for the Management of Mucosal Candidiasis

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
Oropharyngeal: <b>Preferred</b> (7–14 days): Fluconazole 100 mg PO daily Or Clotrimazole troches 10 mg PO 5 × daily Or Nystatin suspension 4–6 ml 4 × daily or 1–2 pastilles 4–5 × daily Or Miconazole mucoadhesive tablet PO daily <b>Alternative:</b> (7–14 days) Itraconazole solution 200 mg PO daily Or Posaconazole oral solution 400 mg 2 × daily for one day, then daily If fluconazole refractory, consider Amphotericin B oral suspension 100 mg/ml 1 ml PO 4 × daily Esophageal: <b>Preferred:</b> (14–21 days) Fluconazole 100 mg (up to 400 mg) PO or IV daily Or Itraconazole oral solution 200 mg PO daily Alternative, or if fluconazole refractory: (14–21 days) Voriconazole 200 mg PO or IV 2 × daily Or Posaconazole 400 mg PO 2 × daily Or Caspofungin 50 mg IV daily Or Micafungin 150 mg IV daily Or Anidulafungin 100 mg IV once, then 50 mg daily Or Amphotericin B 0.6 mg/kg IV daily	Oropharyngeal: (7 days) Nystatin pessaries 100,000 IU sucked every 4 hours Or Nystatin oral suspension 100,000 IU 3 × daily Or Amphotericin B oral suspension 1 spoon 3 × daily Or Miconazole 2% oral gel 2 spoons 3 × daily Esophageal: (14 days) Fluconazole 200 mg daily Or Itraconazole 400 mg daily Or Ketoconazole 200 mg daily	Oropharyngeal: (7–14 days) <b>Preferred:</b> Nystatin 500,000 IU tablet gargled 4–5 × daily Or Clotrimazole troche 10 mg 5 × daily Or Fluconazole 100–200 mg daily <b>Alternative:</b> Itraconazole 100 mg 2 × daily (up to 400 mg per day) Esophageal: (14–21 days) Fluconazole 200–400 mg PO daily Or Itraconazole 200 mg PO daily

Ketoconazole has a high rate of hepatitis and is not recommended unless no alternative available.

Amphotericin B oral suspension not available in USA.

Prolonged maintenance therapy not recommended due to development of resistance.

more common in those with indwelling vascular catheters, or who inject drugs, when candida endophthalmitis may co-exist.

### CRYPTOCOCCAL MENINGITIS (TABLE 117.8)

Cryptococcal meningitis is a common OI, manifesting typically in those with a CD4 count of less than 50 cells/ $\mu$ L, but the clinical signs may be initially subtle. Blood or tissue culture has a high sensitivity, as does serum or CSF cryptococcal antigen. Culture may be used to monitor response to treatment, with a switch to oral medications considered safe if negative at 2 weeks, but serial antigen determination does not predict treatment response. The major mortality and morbidity results from raised intracranial pressure. Serial lumbar puncture or CSF drainage may be necessary until pressures normalize.

If no clinical response occurs within 2 weeks of treatment then consideration should be given to either prolongation of the

current regimen if first line, optimizing drug dosage or switching to an alternative agent such as voriconazole if available. Resistance to amphotericin is rare.

IRIS associated with initiation of ART in patients previously treated for cryptococcal meningitis is particularly common, and may manifest months after treatment. Immediate initiation of ART in patients treated simultaneously with high fluconazole has been shown to be associated with toxicity and mortality. Most experts recommend waiting until stable on maintenance therapy.

### PENICILLIOSIS (TABLE 117.9)

*Penicillium marneffei* is rarely encountered outside the endemic regions of Northern Thailand, Vietnam, and Southern China. Response to initial treatment is usually good, but relapse occurs in 50% of patients without maintenance therapy unless



**Table 117.8:** Recommendations for the Management of Cryptococcal Meningitis

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
<b>Preferred:</b> Induction 2 weeks Amphotericin B deoxycholate 0.7 mg/kg IV daily plus flucytosine 100 mg/kg PO daily in 4 divided doses for at least 2 weeks Or Liposomal amphotericin 4–6 mg/kg plus flucytosine if renal dysfunction present or likely <b>Alternative:</b> Amphotericin as above plus +/- Fluconazole 400 mg PO or IV daily Or Fluconazole 400–800 mg PO or IV plus flucytosine 100 mg/kg PO daily in 4 divided doses for 4–6 weeks if unable to tolerate amphotericin B <b>Preferred:</b> Consolidation Fluconazole 400 mg PO daily for 8 weeks followed by 200 mg daily until immune restoration <b>Alternative:</b> consolidation Itraconazole 200 mg 2 × daily for 8 weeks then 200 mg daily until immune restoration if intolerant of fluconazole	<b>Preferred:</b> Amphotericin B 0.7 mg/kg IV daily for 2 weeks followed by Itraconazole 200 mg 2 × daily or fluconazole 400 mg PO daily for 8 weeks <b>Alternative:</b> Fluconazole 400 mg daily for 8–12 weeks followed by Fluconazole 200 mg daily or Itraconazole 200 mg daily	<b>Preferred:</b> Amphotericin B 0.7 mg/kg/day IV plus Flucytosine 100mg/kg PO 4 × daily followed by Fluconazole 400 mg daily for 8–10 weeks, then 200 mg daily until immune restoration <b>Alternative:</b> Amphotericin B and Flucytosine as above followed by itraconazole 200 mg 2 × daily for 8 weeks Or Fluconazole 400 mg daily for 8 weeks followed by 200 mg daily Or Itraconazole 200 mg PO 3 × daily for 3 days, then 200 mg 2 × daily for 8 weeks Or Fluconazole 400 mg daily plus flucytosine 100 mg PO daily for 8 weeks

Addition of flucytosine is associated with quicker CSF sterilization and less chance of relapse.

Raised intracranial pressure should be actively managed by serial lumbar puncture or CSF shunt until normal.

Risk of IRIS with cryptococcal disease is high and may present several months after initiation of HIV therapy.

Where available and tolerated, fluconazole is preferred to itraconazole.

Amphotericin B may induce renal dysfunction.

Flucytosine can induce hepatitis and bone marrow suppression. Drug levels may be useful when available.

**Table 117.9:** Recommendations for the Management of Penicilliosis

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
<b>Acute infection in severely ill patients:</b> Amphotericin B deoxycholate 0.6 mg/kg/day IV daily for 2 weeks; followed by itraconazole 400 mg PO daily for 10 weeks <b>Mild disease:</b> Itraconazole 400 mg PO daily for 8 weeks <b>Maintenance therapy:</b> Itraconazole 200 mg PO daily	<b>Preferred:</b> Amphotericin B IV (0.7 mg/kg daily) for 2 weeks followed by itraconazole 400 mg orally daily for 8–10 weeks <b>If mild disease,</b> consider Itraconazole 400 mg daily for 8 weeks <b>Maintenance therapy:</b> Itraconazole 200 mg PO daily	<b>Preferred:</b> Moderate-to-severe cases: Amphotericin B 0.6 mg/kg/day × 2 weeks, then itraconazole 200 mg PO bid × 10 weeks <b>Maintenance therapy:</b> Itraconazole 200 mg daily

Fluconazole has less activity against *Penicillium marneffe* than itraconazole.

suppressive ART can maintain a CD4 of greater than 100 cells/ $\mu$ L for over 6 months. Cases of treatment failure may respond to voriconazole.

### ASPERGILLOSIS (TABLE 117.10)

Invasive aspergillosis, usually caused by *Aspergillus fumigatus* is rare, and occurs only in the very immunosuppressed, often after extensive courses of antibiotics and corticosteroids for other infections. Disease may be pulmonary or disseminated.

### HISTOPLASMOSIS (TABLE 117.11)

*Histoplasma capsulatum* infection affects as many as 5% of HIV infected persons living in an endemic area per year. The disease is most common in certain geographical areas of the Southern USA, and in Latin America, where risk factors such as contact with bird or bat droppings and heavy contact with soil should be avoided where possible in the immunosuppressed.

Clinical improvement on therapy should occur after 1 week, and blood or urine antigen titers may decrease thereafter. Treatment

**Table 117.10:** Recommendations for the Management of Aspergillosis

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
<b>Preferred:</b> Voriconazole 6 mg/kg IV 2 × daily for 1 day, then 4 mg/kg IV 2 × daily until clinical improvement followed by Voriconazole 200 mg PO daily  <b>Alternative:</b> Amphotericin B deoxycholate 1 mg/kg/day IV or Lipid formulation of amphotericin B 5 mg/kg/day IV or Caspofungin 70 mg IV × 1, then 50 mg IV daily or Posaconazole 400 mg 2 × daily PO	No specific recommendation	No specific recommendation

Relative paucity of data in the ART era.

Without immune reconstitution the prognosis is very poor.

failure may respond to posaconazole. Secondary prophylaxis should continue for at least one year, but may be stopped in a patient with a fully suppressed viral load on ART, with a CD4 cell count of greater than 150 cells/ $\mu$ L and no signs of ongoing disease. However, because relapse is common, some recommend lifelong secondary prophylaxis.

### Coccidioidomycosis (Table 117.12)

This disease, endemic to the Southwest USA and some areas of Central and Latin America responds slowly to treatment. Relapse is common and secondary prophylaxis should be maintained for life.

## Protozoal Opportunistic Infections

### Toxoplasma Gondii (Table 117.13)

Cerebral toxoplasmosis usually results from reactivation of latent toxoplasma cysts, but may also result from primary infection. It is the commonest cause of cerebral lesions in an HIV positive patient. Treatment should be instituted empirically, and

**Table 117.11:** Recommendations for the Treatment of Histoplasmosis

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
<b>Preferred:</b> Moderate to severe Liposomal amphotericin B 3 mg/kg IV daily for 2 weeks followed by itraconazole 200 mg PO 3 × daily for 3 days then 200 mg 2 × daily  <b>Alternative:</b> moderate to severe Amphotericin B deoxycholate 0.7 mg/kg IV daily or Amphotericin B lipid complex 5 mg/kg for 2 weeks followed by itraconazole as above  <b>Preferred:</b> less severe disease Itraconazole 200 mg 3 × daily for 3 days then 2 × daily  <b>Preferred:</b> Meningitis Liposomal amphotericin 5 mg/kg daily for 4–6 weeks followed by itraconazole 200 mg 2–3 × daily	Amphotericin B 0.7 mg/kg IV daily. Minimum total dose should be 2 g. Followed by itraconazole 200 mg daily for life or until immune recovery on ART	Amphotericin B 0.6 mg/kg IV daily for 2 weeks then itraconazole 200 mg PO 2 × daily for 10 weeks followed by 200 mg daily for life

Itraconazole levels may be useful if available.

Ideally Itraconazole maintenance should continue for at least 12 months and only discontinued after immune restoration.

Itraconazole solution may be better absorbed than capsules.

**Table 117.12:** Recommendations for the Management of Coccidioidomycosis

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
<b>Preferred:</b> mild disease Fluconazole 400 mg PO daily Or Itraconazole 200 mg PO 3 × daily for 3 days then 2 × daily  <b>Preferred:</b> severe, non-meningeal Amphotericin B 0.7–1.0 mg/kg IV daily Or Lipid formulation Amphotericin 4–6 mg/kg IV daily Switch to azole when clinically improved  <b>Preferred:</b> Meningeal disease Fluconazole 400–800 mg PO or IV daily  <b>Maintenance:</b> Fluconazole 400 mg PO once daily Or Itraconazole 200 mg PO 2 × daily	No recommendation	No recommendation

Meningitis may cause raised intracranial pressure.

Maintenance therapy as secondary prophylaxis should be life long.

**Table 117.13:** Recommendations for the Management of Cerebral Toxoplasmosis Infection

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
<b>Preferred:</b> Pyrimethamine 200 mg PO loading dose, then 50 mg (<60 kg) or 75 mg (>60 kg) PO daily plus sulfadiazine 1000 mg (<60 kg) or 1500 mg (>60 kg) PO q6h plus leucovorin 10–25 mg PO daily <b>Duration:</b> 6 weeks or longer if response incomplete <b>Alternative:</b> Clindamycin 600 mg IV or PO q6h plus pyrimethamine/leucovorin as above Or Trimethoprim-sulfamethoxazole 5/25 mg/kg IV or PO 2 × daily Or Atovaquone 1500 mg 2 × daily with or without either or sulfadiazine 1000–1500 mg PO q6h or Azithromycin 900–1200 mg PO daily plus pyrimethamine/leucovorin as above	<b>Preferred:</b> Pyrimethamine 75–100 mg loading dose then 25–50 mg daily plus sulfadiazine 1000 mg q6h plus folic acid 15 mg alt days. <b>Duration:</b> 6 weeks	<b>Preferred:</b> Pyrimethamine 100–200 mg PO loading dose, then 50–100 mg daily plus folinic (or folic) acid 10 mg PO daily plus sulfadiazine 1000–2000 mg 4 × daily <b>Alternative:</b> Trimethoprim-sulfamethoxazole 5/25 mg/kg daily Or Clindamycin 600 mg 3 × daily plus pyrimethamine 100 mg PO loading dose followed by 50 mg PO daily plus folinic acid 10 mg PO daily

Anticonvulsants are not necessary unless history of seizures.

Steroids (e.g., dexamethasone) may be indicated to reduce mass effect from focal lesions.

Renal impairment common with sulfadiazine; ensure adequate fluid intake.

Treatment duration 6 weeks.

Secondary prophylaxis should follow treatment until immune restoration.

further investigations performed if good clinical or radiological response does not occur within the first 2 weeks of therapy. Both clindamycin and sulfadiazine can cause rash or hepatitis, and switching to alternative regimen is recommended if these symptoms persist. Sulfadiazine may crystallize in the urine and cause renal impairment; hence urine output should be greater than 1500 ml/day. Pyrimethamine causes myelosuppression through inhibition of folic acid synthesis. The addition of folinic acid to pyrimethamine-based regimens is therefore essential.

Primary prophylaxis is achieved with 480–960 mg Cotrimoxazole if the CD4 is less than 200 cells/ $\mu$ L, and secondary prophylaxis using lower doses of the treatment regimen should continue until immune reconstitution.

Prevention of *Toxoplasma gondii* ingestion through contamination with cat feces, undercooked red meat, and soil should be advised.

### CRYPTOSPORIDIOSIS (TABLE 117.14)

*Cryptosporidium species* may cause diarrhea and abdominal cramps in immunocompetent as well as immunosuppressed hosts; however, in those with a CD4 count of less than 100 cells/ $\mu$ L, the symptoms may be particularly severe and progress to chronicity. Prior to the advent of ART, it was the commonest pathogen identified in an HIV positive individual with diarrhea.

The mainstay of treatment is supportive with fluid and electrolyte replacement if necessary, and symptomatic treatment of diarrhea. Many antibacterial agents have been used, but with limited success, and the only consistently successful intervention is immune restoration through the initiation of ART.

**Table 117.14:** Recommendations for the Management of Cryptosporidiosis

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
<b>Preferred:</b> Initiate or optimize HAART for effective immune reconstitution Symptomatic treatment of diarrhea Oral or intravenous fluid and electrolyte replacement <b>Alternative:</b> Trial of nitazoxanide 500–1000 mg PO 2 × daily for 2 weeks in addition to measures listed above	<b>Preferred:</b> ART Maintenance of fluid and electrolyte balance Constipating agents such as loperamide 4 mg initially, then 2 mg with each unformed stool to a maximum of 16 mg daily	<b>Preferred:</b> ART Oral or intravenous rehydration Paromomycin 500 mg PO 4 × daily for 2–3 weeks Or Nitazoxanide 500 mg bid PO Or Azithromycin 500 mg PO daily for 5 days <b>Anti-diarrheal agents:</b> Codeine phosphate 30–60 mg 3 × daily or loperamide 2–4 mg 3 or 4 × daily to maximum of 32 mg in 24 hours

Boiling potentially contaminated drinking water for one minute may reduce the ingestion of viable oocysts.

Symptoms often resolve when CD4 greater than 100 cells/ $\mu$ L.



**Table 117.15:** Recommendations for the Management of Microsporidiasis

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
<b>Preferred:</b> Initiate or optimize HAART for effective immune reconstitution For gastrointestinal infection caused by <i>E. bienuesi</i> : Fumagillin 20 mg PO 3 × daily  <b>For non-ocular infection not caused by <i>E. bienuesi</i> or <i>V. corneae</i>:</b> Albendazole 400 mg PO 2 × daily until CD4 >200 cells/μL  <b>For ocular infection:</b> Topical fumagillin 3 mg/ml eye drops. 2 drops every 2 hours for 4 days, then 2 drops daily PLUS albendazole 400 mg PO 2 × daily	No recommendation	<b>Preferred:</b> If disseminated disease: Itraconazole 400 mg PO OD plus Albendazole 400 mg PO 2 × daily

**MICROSPORIDIASIS (TABLE 117.15)**

Microsporidia are a group of related organisms, the commonest species implicated in HIV-related diarrhea are *Enterocytozoon bienusi* and *E. intestinalis*. Ophthalmic infection may occur with some species (e.g., *Vittaforma corneae*), and manifests as a keratitis.

Fumagillin has been shown to be effective for infections caused by *E. bienusi*, and albendazole with infections caused by *E. intestinalis*. If Fumagillin is used, then a response should be anticipated by 4 weeks of therapy. However, symptoms often resolve with an ART-induced increase in CD4 count to greater than 100 cells/μL.

**ISOSPORIASIS (TABLE 117.16)**

Although the typical manifestation of *Isospora belli* infection is 2–3 weeks of self-resolving small bowel diarrhea, it may

**Table 117.16:** Recommendations for the Management of Isosporiasis

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
<b>Preferred:</b> Trimethoprim-sulfamethoxazole 160/800 mg PO 2–4 × daily for 7–10 days or longer if symptoms persist  <b>Alternative:</b> Pyrimethamine 50–75 mg PO daily plus leucovorin 10–25 mg PO daily Or Ciprofloxacin 500 mg PO 2 × daily for 7 days	<b>Preferred:</b> Trimethoprim-sulfamethoxazole 160/800 mg PO 4 × daily for 7 days	<b>Preferred:</b> Trimethoprim-sulfamethoxazole 320/1600 mg 2 × daily or 160/800 mg 4 × daily for 10 days followed by 160/800 mg 3 × daily for 3 weeks  <b>Alternative:</b> Pyrimethamine and folinic acid for 1 month (no dose recommendations)

Rehydration may be necessary.

cause chronic diarrhea and occasionally biliary disease in the immunocompromised. It is predominantly found in the tropics. Relapse is common therefore secondary prophylaxis should be maintained until the CD4 count is greater than 200 cell/μL. Symptoms should improve within 2–3 days of effective therapy.

**Bacterial Opportunistic Infections****MYCOBACTERIUM TUBERCULOSIS (TABLE 117.17)**

Latent *Mycobacterium tuberculosis* infection (TB) reactivation is 80–100 times more common in HIV infected patients, and in endemic areas primary TB is also common. The clinical presentation may differ depending on the CD4 count, but treatment regimens, duration and outcomes are similar to those of HIV negative TB infected patients. The management of TB/HIV coinfection is complex, and reference to local or international guidelines is recommended. Websites for relevant TB treatment guidelines are listed below. The timing of ART in HIV positive individuals is currently controversial. If a patient develops TB whilst taking ART then the ART should be continued, with dose adjustment for drug interactions where necessary. If TB and HIV are diagnosed simultaneously, then TB treatment should be initiated first. The urgency of ART initiation may depend on the CD4 count and risk of HIV disease progression. Current evidence suggests a potential benefit from early rather than delayed ART across most CD4 spectra.<sup>5</sup> The common manifestations of IRIS may cause worsening of symptoms, but overall mortality and morbidity may be improved.

**MYCOBACTERIUM AVIUM COMPLEX (MAC) (TABLE 117.18)**

*Mycobacterium avium* complex is a common cause of fevers, anemia, weight loss, and raised alkaline phosphatase, especially prior to the advent of ART and primary prophylaxis. It appears to be less common in areas where *M. tuberculosis* is endemic.<sup>7</sup> Treatment duration may be required for up to 12 months, and at least until the CD4 count is reliably greater than 100 cells/μL. Response to treatment should occur within 2–4 weeks, and treatment failure is defined by positive blood cultures 4–8 weeks into treatment. ART should be commenced within the first few weeks of treatment, as clearance without immune reconstitution is unlikely. IRIS is common with the initiation of ART, but can be differentiated from treatment failure by the absence of viable micro-organisms. Non-steroidal anti-inflammatory drugs may be useful in symptom control. Primary prophylaxis with azithromycin 1.2 g weekly should be considered in those with a CD4 count less than 50 cells/μL.

**BACILLARY ANGIOMATOSIS (TABLE 117.19)**

The causative organisms of bacillary angiomatosis are *Bartonella henselae* and *B. quintana*. In addition to skin lesions these bacteria may cause fevers, anemia, bony lesions, and peliosis hepatis. Microbiological response to antibiotics is rapid, but clinical

**Table 117.17:** Recommendations for the Management of Mycobacterium Tuberculosis Infection

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
<p><b>Preferred:</b> Refer to CDC TB guidelines available at <a href="http://www.cdc.gov/tb/">www.cdc.gov/tb/</a></p> <p><b>Doses:</b> Weight and dose-frequency dependent—see specific guideline</p> <p><b>Preferred:</b> Initiation 2 months RHEZ (rifabutin can be substitute for rifampicin). Ethambutol can be discontinued if drug resistance testing shows organism sensitive to RHZ. Continuation with RH to complete 6 months of treatment for pulmonary TB, (extend to 9 months if still culture positive at 2 months of therapy or severe extrapulmonary TB) If CNS/bone or joint involvement extend to 9–12 months. A selection of alternative regimens are available if evidence of rifamycin/isoniazid or multi/extensively drug-resistant organism is cultured. See specific guideline.</p>	<p><b>Preferred:</b> Refer to national guidelines</p> <p><b>Alternative:</b> Use WHO treatment recommendations listed below: Latest version available at : <a href="http://www.who.int/tb/en/">www.who.int/tb/en/</a> Directly observed therapy daily recommended, especially in the induction phase, or when R used.</p> <p><b>Doses:</b> Isoniazid 5 mg/kg daily or 10 mg/kg 3 × weekly Rifampicin 10 mg/kg daily or 10 mg/kg 3 × weekly Pyrazinamide 25 mg/kg daily or 25 mg/kg 3 × weekly Streptomycin 15 mg/kg daily or 15 mg/kg 3 × weekly Ethambutol 15 mg/kg daily or 30 mg/kg 3 × weekly</p> <p><b>Regimens:</b> New TB in HIV positive: 2 months HRZE followed by 4 months HR or 6 months HE. If HE used (not preferred option), must be given daily. If sterile facilities permit, E may be replaced with S in induction phase. Advised in cases of meningeal TB. Previously treated smear positive TB: 2 months HRZES followed by 1 month HRZE followed by 5 months HRE Chronic or multidrug-resistant TB—consult specialist for individualized regimen.</p>	<p><b>Preferred:</b> Refer to Revised National TB Control Programme guidelines available at <a href="http://www.tbcindia.org/">www.tbcindia.org/</a></p> <p><b>Doses:</b> Isoniazid 600 mg 3 × weekly Rifampicin 450 mg (600 mg if weight &gt;60 kg) 3 × weekly Pyrazinamide 1500 mg 3 × weekly Ethambutol 1200 mg 3 × weekly Streptomycin 0.75 g 3 × weekly (0.5 g if younger than 50 years).</p> <p><b>Preferred: All directly observed</b> New TB in HIV positive 2 months HRZE 3 × weekly followed by 4 months HR 3 × weekly</p> <p><b>Previously treated TB:</b> 2 months HRZES then 1 month HRZE then 5 months HRE, all 3 × weekly If tuberculous meningitis, miliary TB, bone or joint involvement, continuation phase should continue to complete 12 months of therapy</p>

Abbreviations: R, rifampicin; H, isoniazid; E, ethambutol; Z, pyrazinamide; S, streptomycin.

Continuation phase of HR rather than H is preferred.

Although CDC 2003 guidelines permit intermittent therapy twice weekly this is not recommended in HIV positive individuals in other guidelines due to concerns of treatment failure.

Multiple drug interaction with HIV medications which may require dose adjustment of rifamycin component of TB treatment, and antiretrovirals:

See [www.HIV-druginteractions.org](http://www.HIV-druginteractions.org) for more details.<sup>6</sup>

Rifabutin instead of rifampicin should be used if in combination with boosted protease inhibitor.

Patients receiving isoniazid should receive pyridoxine 25–50 mg PO daily to reduce risk of peripheral neuropathy.

CDC guidelines recommend 6–8 weeks of corticosteroid for CNS disease.

TB is a common cause of paradoxical reaction and immune reconstitution inflammatory disease.

**Table 117.18:** Recommendations for the Management of MAC Infection

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
<p><b>Preferred:</b> Clarithromycin 500 mg PO 2 × daily plus ethambutol 15/mg/kg daily Consider addition of rifabutin 300 mg PO daily (caution-drug interactions with HAART)</p> <p><b>Alternative:</b> Azithromycin 500–600 mg daily plus ethambutol 15/mg/kg daily</p> <p><b>Alternative 3rd and 4th agents include:</b> Amikacin 10–15 mg/kg IV daily Streptomycin 1 g IV/IM daily Ciprofloxacin 500–750 mg PO 2 × daily Levofloxacin 500 mg PO daily Moxifloxacin 400 mg PO daily</p>	<p>Azithromycin 500–600 mg daily, or Clarithromycin 500 mg 2 × daily plus ethambutol 15/mg/kg/daily plus rifabutin 300 mg daily If no MAC therapy available, start ART.</p>	<p>Clarithromycin or azithromycin with ethambutol. Consider a third agent such as rifabutin or ciprofloxacin. No dose recommendations given. MAC perceived to be uncommon in India</p>

Drug resistance testing, if available, should guide therapy.

IRIS common on initiation of ART.

More experience and quicker time to negative cultures with clarithromycin vs. Azithromycin.

Addition of 3rd agent reduces drug resistance development, and should be considered in those with CD4 < 50 or high bacterial loads.

**Table 117.19:** Recommendations for the Management of Bacillary Angiomatosis

CDC-USA <sup>1</sup>	WHO (SE Asia) <sup>2</sup>	NACO-India <sup>3</sup>
<b>Preferred:</b> Erythromycin 500 mg PO or IV 4 × daily for 3 months Or Doxycycline 100 mg PO or IV 2 × daily for 3 months <b>If CNS or severe infection:</b> Doxycycline 100 mg PO or IV 2 × daily +/- Rifampicin 300 mg PO or IV twice daily for 4 months <b>Alternative:</b> Azithromycin 500 mg daily or Clarithromycin 500 mg 2 × daily	<b>Preferred:</b> Erythromycin 500 mg PO 4 × daily <b>Alternative:</b> Doxycycline 100mg 2 × daily Consider addition of rifampicin 300 mg 2 × daily PO if severe disease or immunosuppressed	<b>Preferred:</b> Erythromycin 500 mg PO 4 × daily or doxycycline 100 mg PO or IV for at least 3 months <b>Alternative:</b> Azithromycin 600 mg daily

Jarisch–Herxheimer reaction to treatment may occur within the first 48 hours of treatment.

Pretreatment with an antipyretic may attenuate this reaction.

response is more gradual, with frequent relapses unless immune reconstitution is achieved. Severely immunocompromised individuals should avoid fleas and lice where possible.

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